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# Aspects on gender, quality of life and diastolic function in patients with cardiovascular disease and type 2 diabetes

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Institutet**

Stockholm 2013

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**Aspects on gender, quality of life and diastolic function in patients with cardiovascular disease and type 2 diabetes**

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Printed by Larseries Digital Print  
ISBN 978-91-7549-016-8

*To my parents Lilijana and Donatas*

To see far is one thing, going there is another

*Constantin Brancusi, sculptor*



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# ABSTRACT

## Background

A majority of patients with type 2 diabetes mellitus (T2DM) suffer and die from a cardiovascular disease (CVD). Because of the increasing prevalence of diabetes, it today rivals smoking, hypertension and hypercholesterolemia as a major risk factor for CVD resulting in a need for more attention and further investigations.

## Aims

In patients with T2DM to

1. explore the role of gender on the development of cardiovascular (CV) events and mortality following acute myocardial infarction (MI)
2. analyse the association between self-reported health and survival after acute MI
3. investigate if insulin therapy influences treatment satisfaction and psychological well-being in patients surviving acute MI
4. assess the progress of early signs of left ventricular (LV) diastolic dysfunction

## Prognosis after acute MI

Eight hundred thirty seven men and 416 women with T2DM and acute MI were followed for a median of 2.1 years. Women were older and had higher prevalence of concomitant diseases compared with men. Total mortality did not differ between the genders. The combined endpoint of death and non-fatal MI or stroke was more common among women than men (39% vs. 32%,  $p=0.012$ ). The difference disappeared after adjusting for age.

## Predictive power of self-rated health

Prospective associations between self-rated health reported by Rating Scale (RS) and all-cause mortality, CV death and CV events were assessed in 465 patients with T2DM and acute MI. The RS score predicted CV events (HR; 95% CI 0.87; 0.80-0.95) and all-cause mortality (0.86; 0.76-0.97) in unadjusted analyses. Corresponding HR after adjustment for potential confounders were 0.90; 0.83-0.99 and 0.90; 0.79-1.02 respectively.

## Satisfaction with treatment and psychological well-being

To determine effects of insulin-based treatment the Diabetes Treatment Satisfaction Questionnaire (DTSQ) and the Psychological General Well-being index (PGWB) were administered to 324 patients with T2DM and acute MI at baseline and after 12-months. Insulin treated patients ( $n=197$ ) had a worse risk profile and more co-morbidity at baseline than patients on oral glucose lowering agents ( $n=127$ ). Insulin-based therapy was well accepted. Treatment satisfaction and psychological well-being were similar between patients treated with insulin and oral drugs at baseline. It improved significantly in both groups and remained similar at 12-months.

## Left ventricular diastolic function in patients with T2DM

Paired data from 73 patients with T2DM and no apparent CVD was available for assessment of LV diastolic function. At baseline LV diastolic dysfunction was observed in 38 patients (52%). During follow-up it normalized in 20 (53%) of these patients and remained unchanged in 18 (47%). Of 35 (48%) patients with normal LV diastolic function at baseline 8 (23%) patients developed dysfunction.

## Conclusions

Diabetes specific risk factors contribute to coronary artery disease and impaired myocardial function. Better understanding of the aspects of gender and quality of life may help to identify patients at risk for CV events and mortality and improve their outcomes. Insulin treatment had similar acceptance as oral glucose lowering treatments among patients with T2DM and established CVD and could be started as needed without adding any burden to the patient. Progression of LV diastolic function in patients with T2DM and no other CVD seems to be slower than earlier described and might even regress over time.

# SAMMANFATTNING

## Bakgrund

En majoritet av patienter med typ 2 diabetes mellitus (T2DM) drabbas och avlider till följd av hjärtkärlsjukdom. Den ökande förekomsten av diabetes gör att det, tillsammans med rökning, högt blodtryck och hyperkolesterolemi är en av de viktigaste riskfaktorerna för hjärtkärlsjukdom och därför i behov av ytterligare uppmärksamhet och forskning.

## Syfte

### Att hos patienter med T2DM

1. undersöka genusaspekters betydelse för utvecklingen av kardiovaskulär sjuklighet och dödlighet efter akut hjärtinfarkt
2. analysera sambandet mellan självskattad hälsa och överlevnad efter akut hjärtinfarkt
3. undersöka om insulinterapi påverkar tillfredsställelse med behandlingen och psykologiskt välbefinnande efter akut hjärtinfarkt
4. bedöma utvecklingen av tidiga tecken på diastolisk vänsterkammardysfunktion

### Prognos efter akut hjärtinfarkt

En grupp av 837 män och 416 kvinnor med T2DM och akut hjärtinfarkt följdes under en mediantid av 2.1 år. Kvinnorna var äldre och hade högre förekomst av åtföljande sjukdomar jämfört med män. Det var ingen skillnad i dödlighet mellan män och kvinnor. Risken för kombinationen död, hjärtinfarkt eller stroke var högre hos kvinnor än män (39% vs. 32%,  $p = 0.012$ ) men den ökade risken försvann efter justering för ålder.

### Prognostisk betydelse av självskattad hälsa

Sambandet mellan självskattad hälsa och total eller kardiovaskulär död samt kardiovaskulär sjuklighet utvärderades med hjälp av en Rating Scale (RS) hos 465 patienter med T2DM och akut hjärtinfarkt. I ojusterade analyser förutsågs det skattade RS-värdet förekomst av kardiovaskulär sjuklighet (HR, 95% CI 0.87; 0.80-0.95) och total dödlighet (0.86; 0.76-0.97). Efter justering för samvarierande faktorer var motsvarande HR 0.90; CI 0.83-0.99 och 0.90; 0.79-1.02.

### Tillfredsställelse med behandlingen och psykologisk välbefinnande

Effekten av insulinbaserad behandling undersöktes hos 324 patienter med T2DM och akut hjärtinfarkt. Patienterna fyllde i två frågeformulär, Diabetes Treatment Satisfaction Questionnaire (DTSQ) och Psychological General Well-being (PGWB), vid studiestart och efter 12 månader. Vid studiestart hade insulinbehandlade patienter ( $n=197$ ) en sämre riskprofil och fler parallella sjukdomar än de som behandlades med orala glukossänkande läkemedel ( $n=127$ ). Insulinbaserad terapi var väl accepterat. Tillfredsställelse med behandling och psykologiskt välbefinnande skilde sig inte mellan grupperna vid studiestart och hade ökat i samma omfattning i båda grupperna vid en uppföljande undersökning efter 12 månader.

### Diastolisk vänsterkamarfunktion hos patienter med T2DM

Parade data från undersökningar utförda före och efter  $6.1 \pm 0.9$  år hos 73 patienter med T2DM utan uppenbar hjärtkärlsjukdom analyserades för bedömning av diastolisk vänsterkamarfunktion. Vid studiestart uppmättes nedsatt diastolisk funktion hos 38 patienter (52%). Under uppföljningstiden normaliserades den hos 20 (53%) av dessa och var oförändrad hos 18 (47%). Av 35 (48%) patienter med normal diastolisk funktion vid studiestart utvecklade 8 (23%) diastolisk dysfunktion under studiens gång.

## Sammanfattning

Diabetesspecifika riskfaktorer bidrar till kranskärlssjukdom och nedsatt myokardiell funktion. Ökad förståelse för aspekter gällande genus och livskvalitet kan bidra till tidig identifiering av patienter med risk för hjärtkärlsjukdom och förbättra deras prognos. Behandling med insulin hade samma acceptans som oral glukossänkande behandling hos patienter med T2DM och hjärtinfarkt och bör kunna startas när behov föreligger utan att bli en börda för patienten. Försämringen av diastolisk vänsterkamarfunktion hos patienter med T2DM utan hjärtkärlsjukdom förlöpte långsammare än vad som tidigare beskrivits och kan även förbättras över tid.

# LIST OF ORIGINAL PAPERS

This thesis is based on the following studies, which will be referred to by their Roman numerals.

## I

Venskutonyte L, Malmberg K, Norhammar A, Wedel H, Rydén L.  
Effect of gender on prognosis in patients with myocardial infarction and type 2 diabetes  
J Intern Med. 2010; 268 :75-82

## II

Venskutonyte L, Brismar K, Öhrvik J, Rydén L, Kjellström B.  
Self-rated health predicts outcome in patients with type 2 diabetes and myocardial  
infarction: A DIGAMI 2 sub-study  
Diabetes and Vascular Disease Research 2013; In press

## III

Venskutonyte L, Brismar K, Rydén-Bergsten T, Rydén L, Kjellström B.  
Satisfaction with glucose-lowering treatment and well-being in patients with type 2 diabetes  
and myocardial infarction: A DIGAMI2 QoL sub-study  
Diabetes and Vascular Disease Research 2012; In press

## IV

Venskutonyte L, Jarnert C, Rydén L, Kjellström B.  
Longitudinal development of left ventricular diastolic function in patients with type 2  
diabetes. A 6-year follow-up of the Diabetes And Diastolic Dysfunction trial  
In manuscript

# LIST OF ABBREVIATIONS

BMI - Body mass index  
CABG - Coronary artery bypass graft surgery  
CAD - Coronary artery disease  
CV - Cardiovascular  
CVD - Cardiovascular disease  
DTSQ - Diabetes Treatment Satisfaction Questionnaire  
HbA1c - Glycated hemoglobin  
LA – Left atrium/ atrial  
LV - Left ventricle/ ventricular  
LVDD - Left ventricular diastolic dysfunction  
MI - Myocardial infarction  
NO - Nitric oxide  
NT-proBNP - N-terminal pro hormone of brain natriuretic peptide  
PCI - Percutaneous coronary intervention  
PGWB - Psychological General Well-Being index  
QoL - Quality of life  
RS - Rating Scale  
SI - Signal intensity  
TDI - Tissue Doppler imaging

# INTRODUCTION

## Diabetes

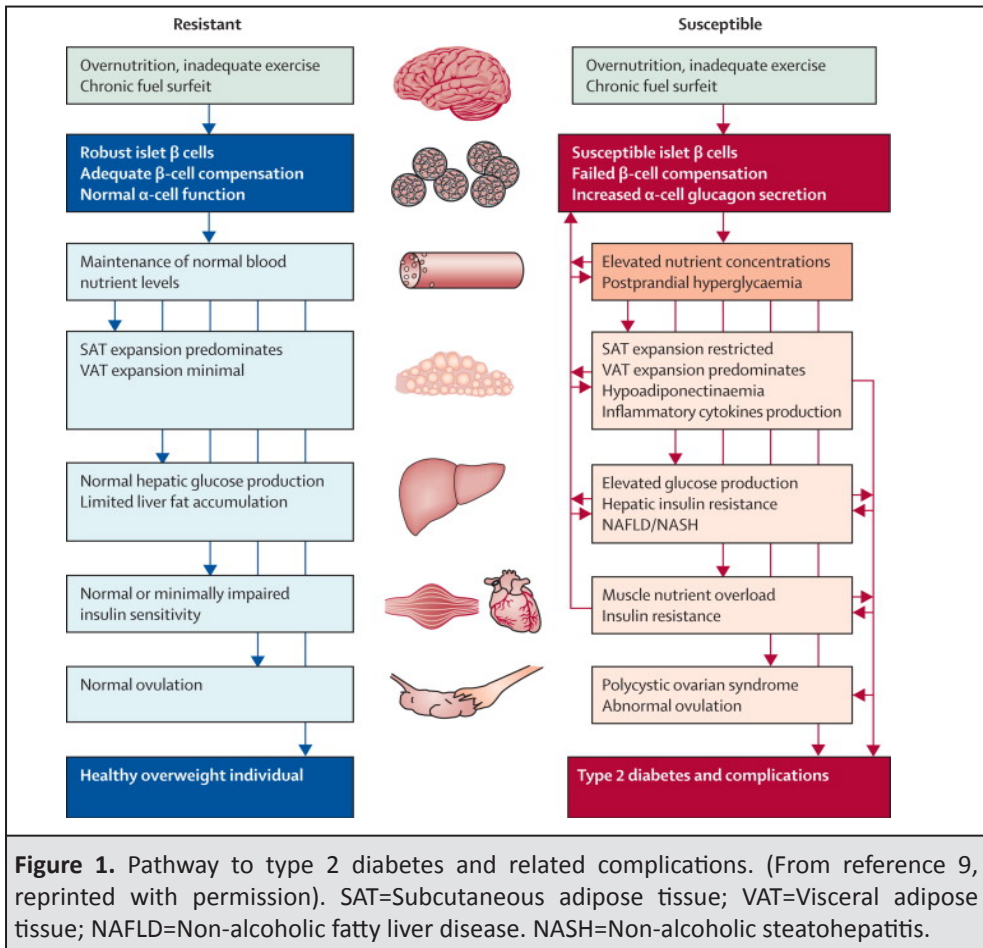
### ***General aspects***

Diabetes mellitus is a chronic metabolic disorder characterized by a high blood glucose concentration (hyperglycemia), resulting either from deficiency of insulin secretion, impaired insulin sensitivity or a combination of both. Diabetes is common, the estimated global prevalence of diabetes is 8% (1) and about one third of these are considered undiagnosed. If current trends continue, approximately 10 % of the global population will have diabetes by 2030, a substantial increase in prevalence depending on urbanization with a less healthy lifestyle and improved longevity (2). The societal costs for diabetes are considerable and increasing (3) and it is estimated that current diabetes related expenses account for 11% of the total global healthcare expenditures (1). Complications to diabetes, predominantly cardiovascular disease (CVD) (4), is a major component of the direct medical costs while disability and increased mortality (1) generate indirect societal and productivity loss expenditures. Apart from growing demands on health care facilities (5) diabetes also may have devastating effects on quality of life (QoL) due to change in patient's self-care behaviors, treatment strategies requiring persistent efforts from the side of the patient and suffering caused by complications as major components. As the prevalence of diabetes is growing, efforts to improve prevention and treatment of the disease are required to reduce the human and economic burden.

### ***Etiology and pathogenesis***

Depending on the pathogenetic mechanisms leading to hyperglycemia, patients with diabetes generally fall into three main categories (6): type 1 diabetes induced by  $\beta$ -cell destruction and absolute insulin deficiency; type 2 diabetes predominantly predisposed by insulin resistance and relative insulin deficiency; other specific types reflecting genetic defects associated with  $\beta$ -cell function and insulin action, pancreatic disease, endocrinopathies, drugs, infections, immune mediated conditions and gestational diabetes. Despite the multiple pathogenetic mechanisms more than 90% of people with diabetes are categorized as having type 2 diabetes (1) with insulin resistance in peripheral tissues and a progressive decline in  $\beta$ -cell function as the main pathophysiological features. People with a genetic predisposition (7) subjected to environmental factors such as aging, lack of physical activity and overweight, in particular with visceral obesity (8), develop a decreased insulin sensitivity. This typically occurs several years prior to the onset of type 2 diabetes when blood glucose still is within the normal range. Given that insulin resistance has been observed in healthy individuals with increased percentage of body fat (Figure 1), it is assumed that combined effects of both factors, insulin resistance and deficient insulin secretion, are important for the development of type 2 diabetes.

Adipose tissue acts like storage of energy in the form of triglycerides. Moreover, it is secreting hormones and cytokines (adipokines) affecting glucose and lipid metabolism (9). In the presence of insulin resistance adipocytes are dysfunctional and start producing more inflammatory cytokines and adipokines leading to chronic inflammation, which interferes with



insulin signaling pathways. Dysfunctional adipocytes also have an impaired ability to take up and release free fatty acids which redirects lipids to peripheral tissues including skeletal muscle (10), liver (11), pancreas and the heart (12). Ectopic fat deposition may interfere with organ function and is associated with whole-body insulin resistance (13). In the presence of insulin resistance, insulin-mediated glucose uptake in the target tissues, primarily skeletal muscles (14; 15) is attenuated. Accompanied by the combination of hepatic insulin resistance and glucose overproduction (16) it leads to rising postprandial glycemia. Compensatory hyperinsulinemia may further decrease the number of insulin receptors impairing insulin sensitivity even more. Eventually, when insulin resistance becomes severe, the  $\beta$ -cells can no longer sustain an insulin secretion of sufficient magnitude to maintain fasting blood glucose levels at a normal level. Failure in  $\beta$ -cell function has been claimed to relate mostly to such mechanisms as a decrease in  $\beta$ -cell mass, toxicity induced by chronic hyperglycemia (glucotoxicity) and disturbed lipid metabolism (lipotoxicity) (17; 18). In  $\beta$ -cells exposed to chronic hyperglycemia secretory granules become depleted and less responsive to further hyperglycemia. In addition, chronically elevated free fatty acids can cause direct damage to the pancreatic  $\beta$ -cells.

Type 2 diabetes is predominantly a disease of middle-aged and older people. However, it is becoming increasingly more common in young people including adolescents and even children who are affected by lifestyle factors leading to increased body weight (19; 20). Type 2 diabetes is a slowly progressing disorder. Its presence may be unrecognized for several years since the time until the onset of symptoms characteristic for diabetes such as tiredness, increased thirst and polyuria is often long. As a result, diabetes is frequently diagnosed with the onset of burdensome and costly complications e.g. myocardial infarction (MI) (21), nephropathy (22) and retinopathy (23).

## ***Diabetes and cardiovascular disease***

### ***General aspects***

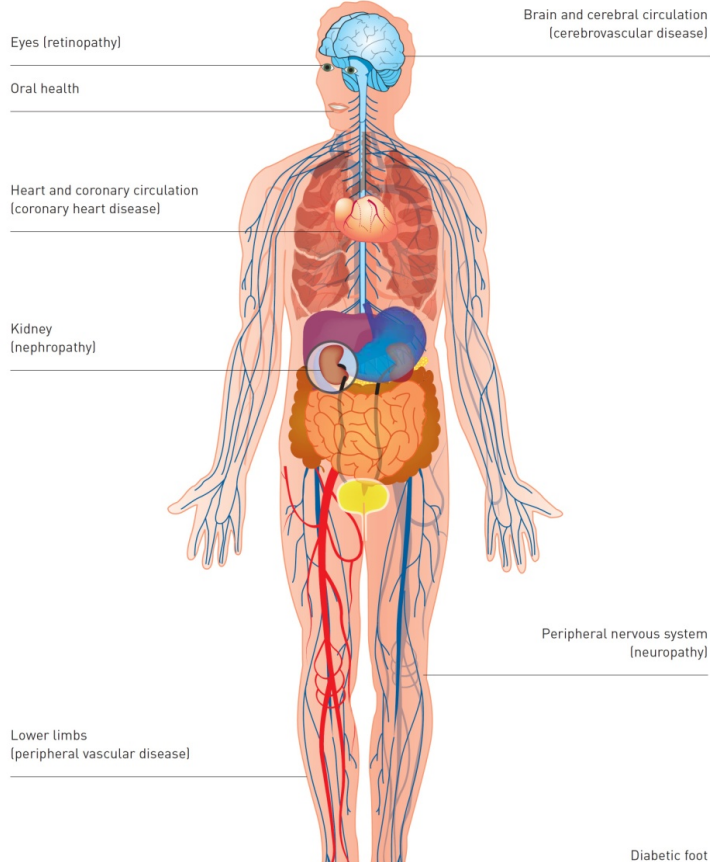
According to estimates by the International Diabetes Federation (IDF) diabetes accounts for 8% of the total global mortality and CVD is behind at least 50% of these deaths (1; 24). The increased risk of cardiovascular (CV) events is already present in the pre-diabetes stage (25). Diabetes and its pre-states are risk factors for a variety of CVD manifestations (26), which can take the format of micro- or macro-angiopathy (Figure 2).

Micro-angiopathy is associated with complications such as retinopathy, nephropathy and neuropathy. However, the most important long-term effects of diabetes is often those related to macro-angiopathy i.e. coronary artery disease (CAD), stroke or peripheral vascular disease (27). Macro-angiopathy is a predominant underlying cause of morbidity and mortality in patients with type 2 diabetes, and as already underlined, often an initial manifestation of this disease. In addition to vascular complications diabetes can induce changes in cardiac structure and function leading to impaired myocardial performance.

### ***The pathophysiological background***

The metabolic perturbations occurring in diabetes, insulin resistance and hyperglycemia provoke vascular dysfunction, trigger atherosclerosis and thus, increase the risk of CV events. The pathophysiology of accelerated atherosclerosis in patients with diabetes is characterized by dysfunction of the endothelium, vascular smooth muscle cells and platelets but also by prothrombotic and proinflammatory states (28; 29). In patients with diabetes endothelial dysfunction is an early manifestation of vascular involvement (30). Endothelial cells synthesize nitric oxide (NO) which plays an important role causing vasodilatation and protecting vessels from endogenous injury (31). It prevents leukocyte and platelet interaction with the vascular wall and inhibits vascular smooth muscle cell proliferation and migration. Hyperglycemia, insulin resistance and fatty acid deliberation that occur in patients with diabetes lead to endothelial dysfunction and deficient NO production (31; 32). This results in monocyte and smooth muscle cell migration from media into the intima and formation of macrophage foam cells promoting atherosclerosis and altered NO mediated vasodilatation. Moreover, dysfunctional endothelial cells synthesize vasoconstrictor prostanoids and endothelin, thus further promoting inflammation, smooth muscle cell contraction and growth. Release of circulating inflammatory cytokines and chemokines also predispose vascular inflammation (33). In addition, patients with diabetes are at increased thrombotic risk which is composed of enhanced platelet adhesion and aggregation, up regulation of pro-thrombotic markers coupled with suppression of fibrinolysis (32).

**Figure 1.1. The major diabetes complications**



**Figure 2. Vascular complications to diabetes and pre-diabetes. (From reference 1, reprinted with permission)**

### *Clinical consequences*

In the presence of diabetes the risk to develop CAD is more than doubled (25), and it is a leading cause of morbidity, decreased QoL and death. In these patients CAD is often silent and more advanced at time of diagnosis (34), which contributes to the more dismal outcome than that seen in subjects without diabetes (35). A previous history of MI increases the incidence of reoccurring coronary events and CV death markedly (36-40). Multivessel CAD, a higher risk factor burden and failure to achieve lifestyle and modifiable risk factor goals (41; 42) are likely explanations. The latter is shown in the European Action on Secondary Prevention by Intervention to Reduce Events survey (EUROASPIRE). It demonstrated that 6-months after a hospitalization for CAD approximately 20% of patients with diabetes continued smoking, 43% were obese, 57% had hypertension and 55% had hypercholesterolemia (41). Thus, better understanding of mortality rates and predictors for unfavorable outcome in patients with diabetes could possibly help identifying individuals at excess risk for CAD.

### *Diabetic cardiomyopathy*

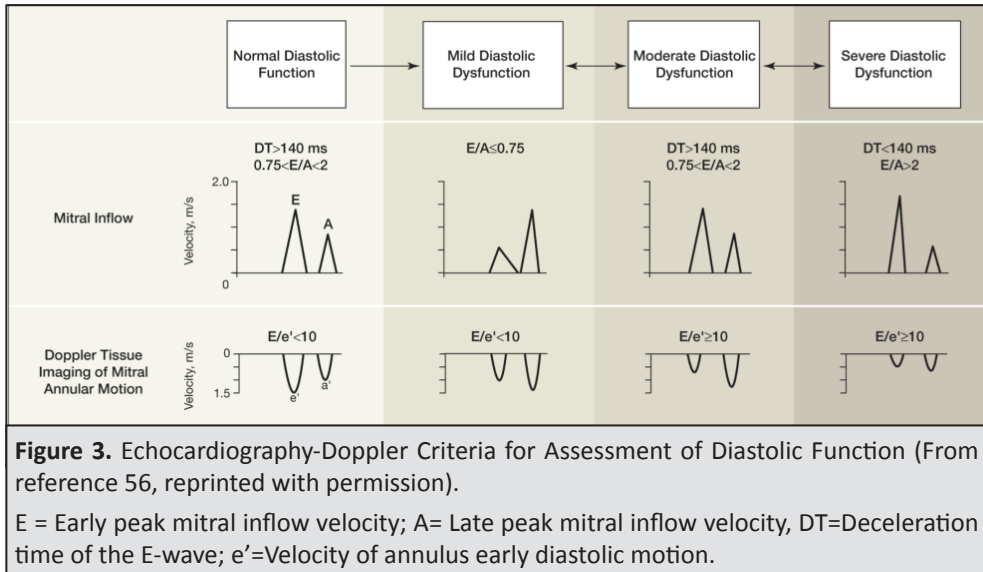
Long-standing hyperglycemia may, even in the absence of CAD, valvular disease or hypertension, increase the risk of myocardial dysfunction, a state known as “diabetic cardiomyopathy”. The first to introduce this term were Rubler *et al.* (43), who in 1972 reported on postmortem findings from four patients with heart failure but no signs of CAD. Since then the concept of diabetic cardiomyopathy has been supported by studies, including larger number of patients, confirming the existence of left ventricular (LV) dysfunction in the absence of ischemia or other evident CVD in patients with diabetes (44-47).

The pathogenesis of diabetic cardiomyopathy is multifactorial but not completely understood. It is known that it involves accumulation of advanced glycation end products, enhanced collagen formation and interstitial fibrosis (48), disturbances in adipokine secretion and signaling (49) leading to impaired calcium homeostasis, impaired myocardial insulin signaling (50) and lipotoxicity (51). All these perturbations cause changes in the myocardial structure, among them LV hypertrophy and increased myocardial stiffness that compromises the function of the heart by reducing myocardial compliance (52-54). LV diastolic dysfunction (LVDD) in the form of impaired myocardial relaxation is considered to be an early sign of diabetic cardiomyopathy.

### *Assessment of left ventricular diastolic dysfunction*

According to the European Society of Cardiology (ESC) recommendations, LVDD is identified by quantitative estimation of LV diastolic properties using conventional Doppler variables of the transmitral inflow of blood and tissue Doppler imaging (TDI) of the mitral annulus (55). Deteriorating LVDD is associated with a progressive increase in LV filling pressures, which have an impact on the transmitral flow pattern. In a healthy and compliant heart the left atrial (LA) pressure in early diastole exceeds the LV pressure and accelerates passive transmitral flow. Thus, the E-component of the atrial pressure occurring during early diastolic transmitral flow is greater than the subsequent A-wave occurring during late diastolic transmitral flow. This is expressed as the E/A ratio where  $E > A$ . Impaired LV relaxation, accompanied by progressively increasing LV filling pressures, is associated with a reduced E and increased A diastolic transmitral flow velocity causing a reversal of the E/A ratio (Figure 3). This contributes to elevated LA pressure and increased E-velocity as relaxation becomes further impaired (56). During its early phases, this may cause the inflow pattern to resemble a normal diastolic filling pattern, referred to as pseudonormalisation. To distinguish between pseudonormalisation and a normal mitral inflow profile a Valsalva maneuver is used (57; 58) which reduces preload to the LV and helps to differentiate between patients with high filling pressures from those with normal filling pressures. As LV function continues to deteriorate, the LV compliance decrease and LA pressure increase leading to an increased transmitral gradient identified by a high E velocity, low A velocity and an inverted E/A ratio, typically larger than 2.

Early ( $e'$ ) and late ( $a'$ ) diastolic mitral annular velocities obtained by pulsed TDI add to the evaluation of LV myocardial performance. TDI is considered a more reliable measure of LVDD than transmitral flow measurement (59). The  $e'$  velocity reflects myocardial relaxation and the  $e'$ -wave is decreased throughout all stages of LVDD while the E-wave first decreases and then increases. Thus, the  $E/e'$  ratio increases progressively with increasing LV filling pressures. For an accurate evaluation of LVDD it has been recommended to use a combination of several echocardiographic criteria (55).



Echocardiographic investigations revealed that 46-75 % of patients with diabetes but without known CVD had signs of LVDD (60-62). The variation in prevalence relate to several factors of which the most important are the definition of LVDD, echocardiographic techniques and the studied population. Diastolic filling abnormalities have been shown to be independently predictive of the development of subsequent heart failure (63; 64) and increased mortality (65; 66). Thus, studies of early stages of diabetic cardiomyopathy become increasingly important for the understanding of a potential propensity of a progression towards symptomatic myocardial dysfunction.

## Quality of life

Health related QoL represents the burden placed on feeling of health by a disease and is an indicator of a person's ability to function in daily life. There is an association between self-reported QoL and an individual's capacity to cope with their disease (67). Moreover, self-reported QoL has been acknowledged as a potent predictor of outcomes including morbidity, hospitalizations and mortality among patients with different chronic illnesses (68-74). Diabetes is a long-term disease with a notable impact on physical, mental and social domains of health related QoL (75; 76). Patients with diabetes who are free from complications usually rate their QoL only slightly lower than age matched peers from the general population (77), but QoL decreases dramatically once the long-term complications appear (77-81). Then the burden of diabetes approaches that experienced by patients suffering from other chronic diseases such as cancer and chronic respiratory disease (82). Although generating significant health benefits and decreasing the risk of harmful complications (83) comprehensive treatment of diabetes, including injected medications, may also decrease QoL (67; 78; 84). Thus, it may affect patients dedication, self-efficient behavior (67) and thereby the compliance to and effects of treatment. Better understanding of health related QoL and treatment satisfaction in patients with diabetes may provide further insights of value for the successful management of the disease, treatment adherence and prediction of future outcome.

## Gender

Risk factors carry different predictive value depending on gender and diabetes has been suggested as a more powerful risk factor in women than in men (64; 85). Women with diabetes have a higher relative morbidity due to CAD and LVDD (86), increased mortality (87) and a worse QoL (88) compared to men. Even if not fully understood, one reason for the increase in CVD risk in women with diabetes may be their heavier risk-factor profile that includes higher prevalence of obesity, elevated blood pressure and dyslipidemia. (89). Moreover, the presence of diabetes may increase the burden of classical risk factors differently depending on gender (89). Diabetes related LVDD has been reported as more prevalent among women compared with men (90; 91). Thus it is important to account for gender-specific discrepancies when managing patients with diabetes. Yet, studies providing insight into this question in patients with diabetes and coexisting comorbidities such as CAD or diabetic cardiomyopathy are sparse. Identification of gender-specific disease-related factors could possibly help to outweigh the negative effects seen in women.

# AIMS

1. To explore the role of gender on the development of cardiovascular events and mortality following acute myocardial infarction in patients with type 2 diabetes  
**(Study I)**
2. To analyse the association between self-reported health and survival in patients with type 2 diabetes and myocardial infarction  
**(Study II)**
3. To investigate if insulin therapy influences treatment satisfaction and psychological well-being in patients with type 2 diabetes and myocardial infarction  
**(Study III)**
4. To assess the progress of early signs of left ventricular diastolic dysfunction in patients with type 2 diabetes  
**(Study IV)**

# PATIENTS AND METHODS

## Studies I-III

### The DIGAMI 2 study (Study I)

Studies I, II and III used material from the second Diabetes Mellitus Insulin-Glucose Infusion in Myocardial Infarction Trial (DIGAMI 2) (92), a prospective, randomized study comprising 1253 patients with type 2 diabetes hospitalized due to suspected acute MI. DIGAMI 2 was conducted in 44 coronary care units in Sweden, Denmark, Norway, Finland, UK and The Netherlands. The aim of the study was to explore whether an acutely introduced, long-term insulin treatment compared with conventional management would improve survival in patients with type 2 diabetes who experienced a MI.

Inclusion criteria were established type 2 diabetes or an admission blood glucose  $>11.0$  mmol/L, suspected acute MI due to symptoms (chest pain 15 min during the preceding 24 h) and/or recent ECG signs (new Q-waves and/or ST-segment deviations in two or more leads). Exclusion criteria were inability to cope with insulin treatment, residence outside the hospital catchment area, participation in other studies or previous participation in DIGAMI 2. Participants were randomized to one of three different glucose-lowering strategies: Group 1) acute insulin-glucose infusion for at least 24 hours followed by multidose insulin in the long term; Group 2) insulin-glucose infusion acutely followed by standard therapy in the long term; Group 3) control patients given glucose-lowering treatment according to local practice. The non-randomized treatment was as uniform as possible and in accordance to evidence-based international guidelines for acute MI and CVD prevention (93). No significant difference in glucose control, total mortality or non-fatal MI and stroke was observed between the three groups during the median follow-up period of 2.1 years.

### *Laboratory methods*

Random blood glucose was obtained as soon as possible after hospital admission. Fasting blood glucose was recorded daily until hospital discharge and at each follow-up visit. Data are reported as whole blood glucose in mmol/L. Glycated hemoglobin (HbA1c) was analysed using high-performance liquid chromatography at a core laboratory (Department of Laboratory Medicine, Malmö Hospital, Sweden) on capillary blood applied to filter paper with an upper normal limit of 5.3% (Boehringer Mannheim Scandinavian AB, Bromma, Sweden) (94). Routine laboratory specimens including fasting blood glucose were analysed locally.

### *Follow-up*

Patient recruitment started in January 1998 and ended in May 2003, minimum follow-up was six months and maximum three years (median 2.1, interquartile range 1.0-3.0 years). Study participants were seen as outpatients after 3, 6, 9 and 12 months and every 6 months thereafter. No patient was lost to follow-up. From the time of the index MI all patients were followed for all-cause mortality, CV death and non-fatal re-infarction or stroke. The diagnosis of acute MI was based on the joint recommendations of the ESC and American College of Cardiology (ACC) (95). Re-infarction was defined as an event  $>72$  h from the index MI. Stroke was defined as unequivocal signs of focal and global neurological deficit of sudden

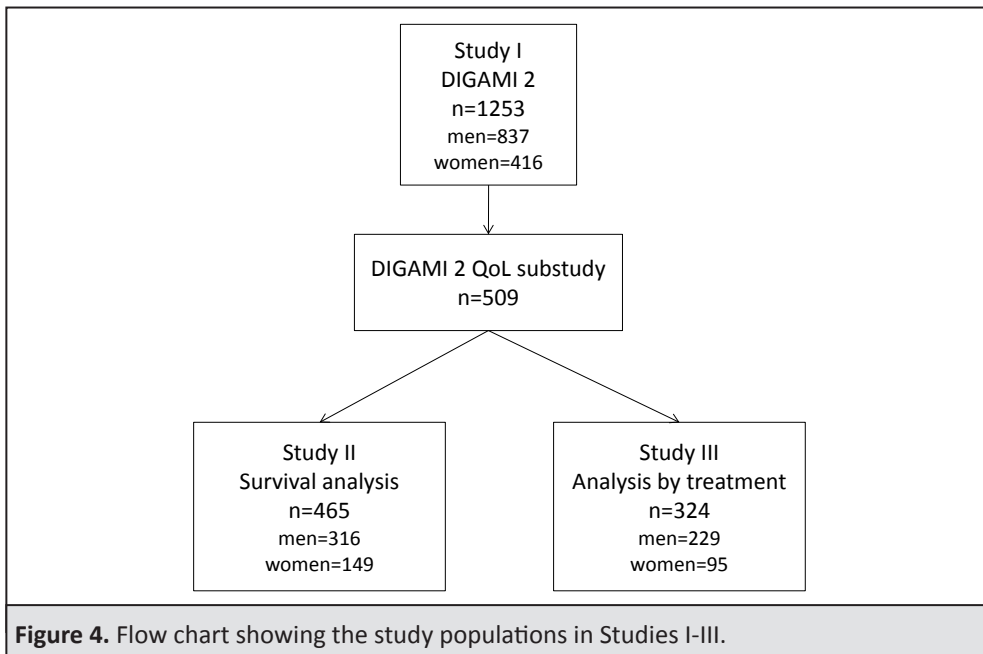
onset and duration of exceeding 24 h that were judged to be of vascular origin. An independent committee composed of three experienced cardiologists adjudicated all the events blindly.

### DIGAMI 2 QoL substudy (Studies II-III)

Studies II and III were based on the predefined DIGAMI 2 Quality of Life substudy (Figure 4). The QoL substudy population consisted of 509 patients from 28 centers in Denmark (n=68), Finland (n=30), Norway (n=63) and Sweden (n=348).

The primary objective of the study was to determine whether a change from conventional intensive insulin-based glucose lowering treatment influenced satisfaction with diabetes treatment and psychological well-being. A secondary objective was to generate evaluations of health states and compare them between treatment groups. The tools used were the Diabetes Treatment Satisfaction Questionnaire (DTSQ), the Psychological General Well-being index (PGWB) and the Rating Scale (RS). All questionnaires were self-administered and filled in by patients prior to hospital discharge and before starting insulin (baseline) and at the 12 months follow-up visit.

*Diabetes Treatment Satisfaction Questionnaire* measures the experience of diabetes treatment including ease of use, side effects and efficacy (96). No other care is evaluated. The tool can be used for both type 1 and type 2 diabetes and for all diabetes treatments and has been validated and recommended by World Health Organization (WHO) and IDF (97). The DTSQ consists of six items assessing treatment satisfaction and two items assessing patient perceived frequency of symptomatic hyper- and hypoglycemia. Each item is rated on a Likert-type scale graded from 0 to 6. The total score reflecting treatment satisfaction is 36 points. A high score represents high satisfaction and vice versa. Questions assessing hyper- and hypoglycemia are evaluated separately and a score of 0 means never while a score of 6 means always.



*The Psychological General Well-Being index* is an epidemiological measure of health-related QoL, developed to provide a frequency and intensity measure of subjective well-being or distress. It is focused on aspects of mental health (98) and has been applied and evaluated in randomized clinical studies (99; 100). It consists of 22 questions divided equally between positive and negative aspects and evaluates six dimensions of well-being: anxiety, depressed mood, vitality, general health, self-control and well-being. Each item is rated on a 6-graded scale and evaluated by the total score of all questions. The highest possible score is 132 and a high number means a greater feeling of well-being. The composite score in each dimension of PGWB may also be evaluated.

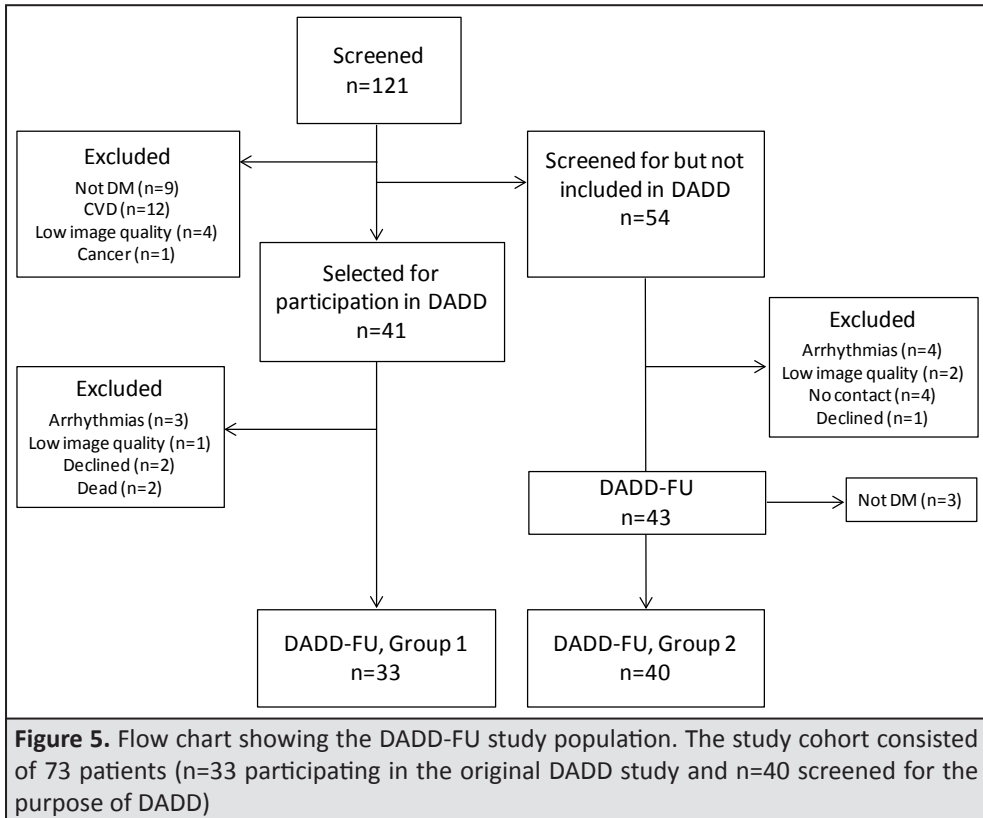
*The Rating Scale* is a preference-based measurement tool using a simple technique for assigning a numerical value for a certain health state in relation to perfect health or death. It consists of a Visual Analog Scale (VAS), a straight vertical line numbered from 0 to 100 where 0 is death and 100 is perfect health. Patients are asked to mark their current state of health on the vertical line which spans from perfect health to death (101).

Study II assessed the data from the patients who completed both RS and PGWB questionnaires at baseline. The association between RS, PGWB scores and CV events and mortality were evaluated. Data from patients who correctly filled in DTSQ, PGWB and RS questionnaires both at baseline and at the 12-months of follow-up was used for the purpose of Study III. In Study III patients treated with insulin at the time of hospital discharge were compared to patients using oral glucose lowering agents.

### **The DADD-FU study (Study IV)**

Study IV was an extended follow-up of the Diabetes mellitus And Diastolic Dysfunction study (DADD), a randomized, prospective trial that investigated the impact of strict glycemic control on myocardial diastolic function in patients with type 2 diabetes and LVDD (102). To be included in DADD the following criteria were to be fulfilled: type 2 diabetes (fasting plasma glucose  $\geq 7.0$  mmol/L or HbA1c  $> 5.5\%$  [Mono-S]), age 40-70 years, normal systolic function and impaired diastolic function according to criteria outlined by the Mayo clinic (66; 103; 104). Exclusion criteria comprised on-going insulin treatment, clinical signs of ischemic heart disease defined as angina pectoris or previous or ongoing MI, peripheral vascular disease, heart failure, atrial fibrillation, clinically significant valvular disease, poorly controlled hypertension, signs of LV hypertrophy (septal wall thickness  $> 13$ mm) or echocardiographic recordings of poor quality. Out of the 121 screened patients 41 were randomized to intensive glucose control by means of either insulin or oral glucose lowering treatment. By the end of the follow-up period intensive glycemic control had not influenced LVDD or myocardial perfusion reserve in either of the two treatment groups.

The DADD follow-up study (DADD-FU) was conducted between September 2010 and March 2012, six years after the completion of DADD. Of the initially screened population all randomized patients (group 1;  $n=41$ ) and 54 subjects who were screened but not randomized (group 2) were invited to participate in DADD-FU. As outlined in Figure 5 the DADD-FU finally comprised 73 subjects. Apart from acceptance of insulin treatment the inclusion and exclusion criteria were the same in DADD-FU as in the original study. Baseline data in DADD-FU were those obtained at the last study visit in DADD (Group 1) or at the occasion of screening (Group 2) respectively.



### Study investigations and laboratory methods

Patients screened for the original DADD trial underwent blood tests (fasting plasma glucose, HbA1c and S-creatinine), transthoracic Doppler echocardiography and TDI at baseline. In addition those who subsequently were randomized underwent the following investigations: medical history, physical examination including blood pressure, supplementary blood tests (blood lipids and N-terminal pro hormone of brain natriuretic peptide [NT-proBNP]) and myocardial contrast echocardiography both at baseline and follow-up. HbA1c was analysed by high performance liquid chromatography presented as Mono S with a measurement interval of 2.9-17.2 %, reference value <5.3%. Mono S HbA1c =  $0.989 \times \text{International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) HbA1c} + 0.88\%$ ;  $r^2=0.996$ ; National Glycohemoglobin Standardization Program (NGSP) HbA1c =  $0.915 (\text{IFCC- HbA1c}) + 2.15\%$  ( $r^2=0.997$ ) (105).

### Assessment of myocardial function

The echocardiographic investigations were performed according to standards outlined by the American Society of Echocardiography (106). LV systolic function was evaluated by calculating the wall motion index (WMI) using a 17-segment model (107) and considered normal if  $\text{WMI} \leq 1.1$ . Diastolic function was assessed by one or more of the criteria listed in Table 1.

<b>Table 1.</b> Echocardiographic measures of left ventricular (LV) diastolic dysfunction.	
<b>Criteria</b>	<b>Clinical implications</b>
E/A <0.75	Delayed LV relaxation
E/A decrease by 0.5 after Valsalva	Pseudonormal LV filling
e' at septal wall <8 cm/s	Delayed LV relaxation
E/e' >15	High LV filling pressure
E/A 0.75-1.5 in combination with LA volume index >32 ml/m <sup>2</sup>	Delayed LV relaxation, increasing LV filling pressure, high pressure in LA
E/e' 8-15 in combination with E/A >1.5 and LA volume index >32 ml/m <sup>2</sup>	Delayed LV relaxation, increasing LV filling pressure, high pressure in LA

### *Myocardial contrast echocardiography*

Patients were studied using low mechanical index myocardial contrast echocardiography (MCE) before and after the administration of dipyridamol (0.84 mg/kg). Micro-bubble replenishment images were recorded in apical six-chamber views as clips comprising 250 frames at 20 frames/s resulting in an acquisition time of 12.5 s. Micro-bubble destruction was set at a mechanical index of 1.9 and standardized to one heart cycle. No post-processing was used. Image loops were collected, stored digitally and analysed on a workstation with dedicated software. Region of interest was manually traced at end-systolic frames in four-chamber view limited to the septal wall excluding the most basal part to avoid less well reproduced areas due to uneven ultrasound intensity and attenuation artifacts. End-systolic frames were analysed and signal intensity (SI) expressed as log compressed data during contrast replenishment fitted to an exponential function giving the two primary components of myocardial flow: the initial slope providing a measure of flow velocity and SI-plateau that correlates to myocardial capillary blood volume (108). Additional region of interest was manually placed in the LV cavity, close to the septum, to measure blood pool SI. After log decompression the SI plateau was normalized for the blood pool SI to obtain a myocardial blood volume index.

## **Data analysis**

### **Study I-IV**

Continuous variables are presented as mean and standard deviation or as median and first-third quartiles. A Student's t-test (Study I) or the Wilcoxon Mann-Whitney rank sum test was used for the comparison between continuous data. Categorical variables are expressed as counts and proportions and Fisher's exact test was used for the comparison between the values. Change in values over time was determined using Student's t-test. A two-sided p-value <0.05 was considered statistically significant. In survival analyses Cox proportional hazard regression was used. Potential confounders for the Cox regression analyses were chosen from univariable analyses accepting those with a p-value <0.05. For illustration purposes, Kaplan-Meier survival plots were presented. Minitab version 13.32 and 16 and SAS 8.02 and 9.2 was used for analyses.

### **Study II-III**

The RS score was included in the analysis if the score was clearly marked with a cross or vertical line across the scale. Patients that used a circle or more than one cross to mark the line were excluded. The DTSQ and PGWB questionnaires were analysed if  $\geq 60\%$  of questions had been answered. A mean imputation method was used to replace missing values in individual questionnaires with the mean value from the whole population before calculating the respective individual total score. For methodological reasons patients, who were not treated with any glucose lowering agents, were excluded from the analysis of treatment satisfaction (DTSQ). In Study III patients who changed treatment from oral to insulin or vice versa during the follow-up period were also excluded. Self-reported hypoglycemia was only analysed in patients who were on glucose lowering treatment.

### **Study IV**

Data analysis was performed separately in the two groups, Group 1 with full data set (n=33) and Group 2 with partial data (n=40) at the time of screening. Intragroup analyses of characteristics and echo measurements were performed based on LV function at follow-up. Patients in Group 1 with remaining LVDD were compared to those who normalized their LV diastolic function while in subjects in Group 2 with remaining normal LV diastolic function were compared to those who developed LVDD. Five patients in Group 2 with known LVDD at baseline were excluded from this analysis.

### **Ethics**

All the studies were conducted according the Declaration of Helsinki and the protocols were approved by the local ethics committee review boards. All patients gave their signed consent to participation following oral and written information on the study protocols.

# RESULTS

## Study I

### Patient characteristics

The DIGAMI 2 study recruited 837 men and 416 women. Baseline clinical characteristics by gender are presented in Table 2. Women were significantly older, more likely to report a history of previous heart failure and hypertension and had lower glomerular filtration rate and higher cholesterol. Smoking and previous coronary artery bypass graft surgery (CABG) were more common among men. The rate of revascularisation procedures during the hospital stay (Percutaneous Coronary Intervention (PCI), CABG or thrombolysis) did not differ between genders. Pharmacological treatment, including glucose lowering drugs, was similar between genders throughout the study with the exceptions that men more often were prescribed aspirin at baseline (52% vs. 46%,  $p=0.043$ ) and at follow-up (85% vs. 77%,  $p=0.045$ ) and women

**Table 2.** Baseline characteristics in Study I. Data are expressed as mean $\pm$ SD or number (%) if not otherwise stated.

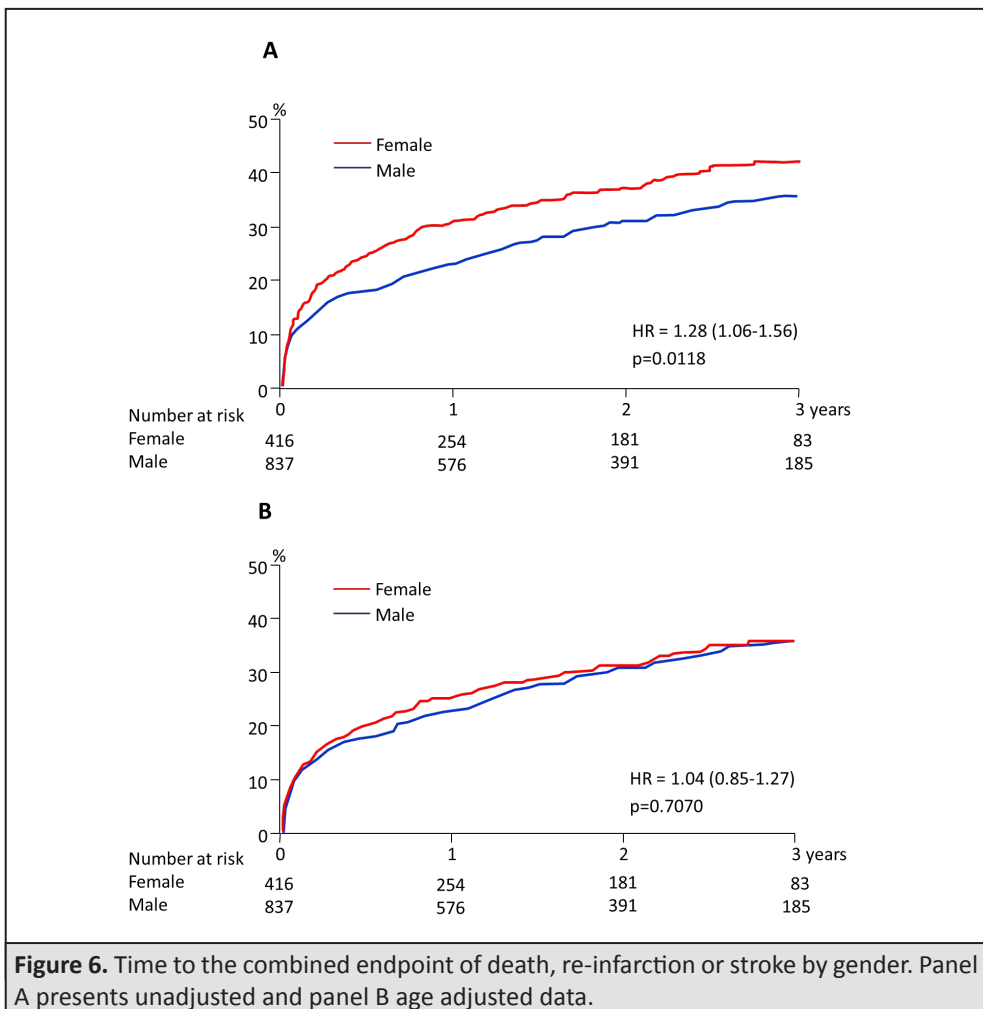
Variable	Male n=837	Female n=416	p-value
Age (years)	67 $\pm$ 11	71 $\pm$ 11	<0.001
Body Mass Index (kg/m <sup>2</sup> )	28 $\pm$ 4	29 $\pm$ 5	0.210
Smokers	212 (26)	88 (22)	<0.001
Diabetes duration (years)	8 $\pm$ 8	8 $\pm$ 9	0.400
Diabetes complications	144 (17)	68 (16)	0.760
Previous			
Heart failure	126 (15)	94 (23)	0.002
Hypertension	384 (46)	223 (54)	0.013
Myocardial infarction	297 (36)	126 (30)	0.076
CABG	111 (13)	25 (6)	<0.001
PCI	75 (9)	25 (6)	0.084
Randomisation B-glucose (mmol/L)	12.7 $\pm$ 4.5	12.7 $\pm$ 4.5	0.977
HbA1c (%)	7.8 $\pm$ 1.7	7.7 $\pm$ 1.9	0.670
Total cholesterol (mmol/L)	5.0 $\pm$ 1.2	5.4 $\pm$ 1.3	<0.001
Creatinine clearance (ml/min)	84 $\pm$ 103	60 $\pm$ 30	0.001
Index infarction			
Time symptoms to admission (hours)	4.3 $\pm$ 4.6	4.6 $\pm$ 4.6	0.310
Q-wave	363 (45)	160 (41)	0.148
Non-Q-wave	348 (44)	188 (48)	0.215

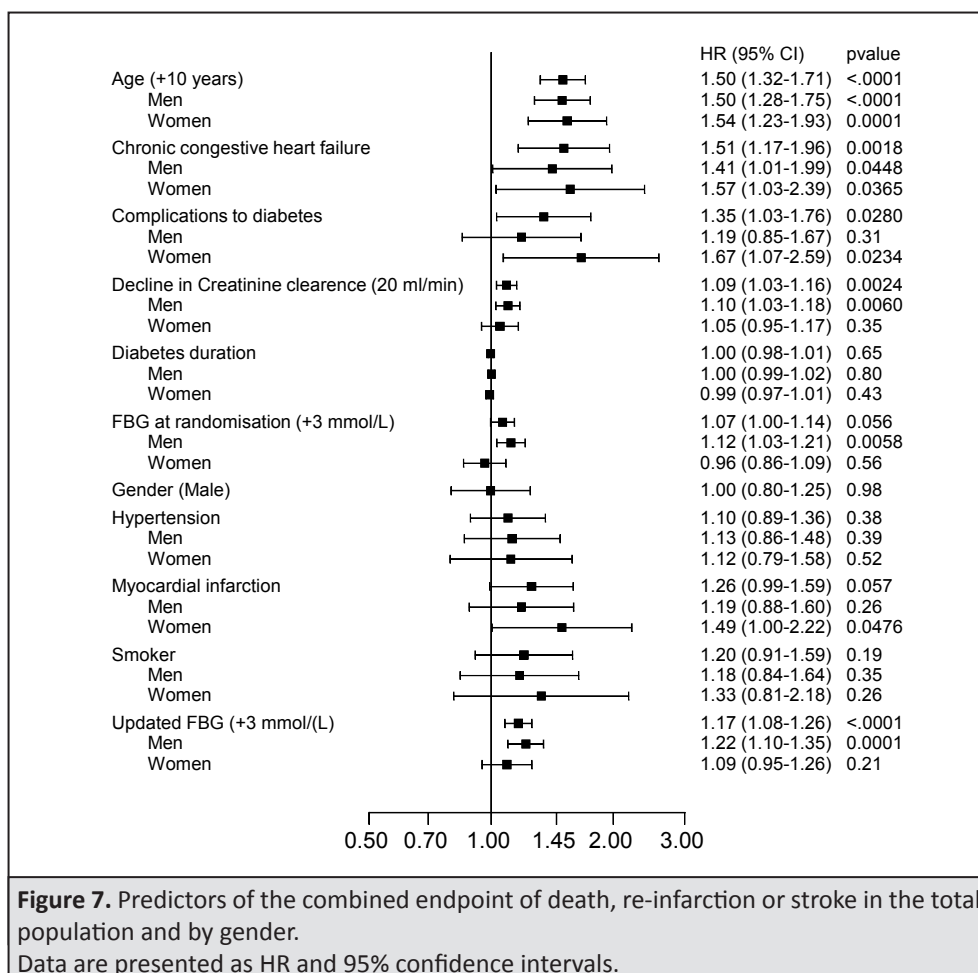
CABG = Coronary artery bypass graft surgery; PCI = Percutaneous coronary intervention; HbA1c = Glycated hemoglobin

were prescribed more diuretics during the total study period. No differences in fasting blood glucose or HbA1c were observed at baseline, at hospital discharge or after two years of follow-up between men and women.

### Morbidity and mortality

No gender difference was observed in numbers of re-infarction, mortality rate or cause of death. The combined endpoint of death, non-fatal MI or stroke was more common among women but this difference disappeared after adjustment for age (Figure 6). Age and prior heart failure were independent predictors of the combined endpoint, shared by men and women. Previous MI and complications of diabetes were independent predictors of increased risk only among women while increased blood glucose at randomization and during follow-up only enhanced the CV risk in men (Figure 7). The hazard ratio for CV events in different age groups for women compared with men was < 65 years HR (95%CI); 1.11 (0.69-1.77), 65-74 years; 0.82 (0.54-1.23), > 74 years; 1.17 (0.90-1.53).





## Study II

### Patient characteristics

The study cohort consisted of 465 patients (median age was 68 years, 68% males) successfully completing the RS and PGWB questionnaires (correctly marked RS score and  $\geq 60\%$  of PGWB questions answered) at baseline. Baseline characteristics for the whole group and by gender are shown in Table 3. Women reported significantly lower RS scores compared to men while there was no gender difference in the total PGWB scores. Two hundred ten patients had RS scores below and 255 above median. Patients with RS scores below median had a higher prevalence of hypertension (43% vs. 54%,  $p=0.019$ ), heart failure (24% vs. 13%,  $p=0.003$ ), previous CABG (16% vs. 10%,  $p=0.049$ ) and had lower PGWB scores (median (interquartile range): 76 (72-81) vs. 79 (76-82),  $p < 0.001$ ). The median duration of follow-up was 2.1 years (interquartile range 1.0–3.0).

### Morbidity, mortality and risk predictors

During the course of the study, 132 (28%) participants experienced a CV event, 71 (15%)

**Table 3.** Baseline characteristics in Study II. Data expressed as median (first-third quartile) or number (%).

Variable	All (n=465)	Men (n=316)	Women (n=149)	p-value
Age (years)	68 (59-74)	65 (58-72)	71 (64-78)	<0.001
Diabetes duration (years)	6 (2-13)	6 (2-12)	6 (1-13)	0.709
Body mass index (kg/m <sup>2</sup> )	28 (26-31)	28 (26-31)	28 (25-31)	0.700
Smokers	116 (25)	80 (25)	36 (24)	0.774
History of				
Myocardial infarction	168 (36)	122 (39)	46 (31)	0.106
Heart failure	88 (19)	56 (18)	32 (22)	0.335
Hypertension	229 (49)	141 (45)	88 (59)	0.004
CABG	64 (14)	52 (17)	12 (8)	0.014
PCI	44 (10)	34 (11)	10 (7)	0.164
Hyperlipidemia	148 (32)	108 (34)	40 (27)	0.114
Insulin treatment	147 (32)	96 (30)	51 (34)	0.405
HbA1c (%) <sup>†</sup>	7.2 (6.3-8.5)	7.2 (6.2-8.4)	7.1 (6.4-8.6)	0.700
Randomisation B-glucose (mmol/L)	12.1 (9.6-14.0)	12.3 (9.5-14.8)	11.8 (9.6-14.5)	0.622
Creatinine clearance (mL/min) <sup>††</sup>	73 (53-92)	79 (59-98)	59 (43-80)	<0.001
Cholesterol total (mmol/L)	5.2 (4.4-6.0)	5.0 (4.3-5.9)	5.4 (4.7-6.3)	0.001
Triglycerides (mmol/L)	1.8 (1.3-2.7)	1.8 (1.2-2.9)	1.8 (1.3-2.6)	0.590
RS score	70 (50-80)	70 (55-80)	65 (50-80)	0.045
PGWB score	78 (74-82)	79 (74-82)	77 (72-81)	0.161

<sup>†</sup> DCCT (Diabetes Control and Complications Trial) HbA1c targets of 6.5% -7.5%

<sup>††</sup> Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault calculator available at [http://nephron.org/cgi-bin/MDRD\\_GFR/cgi](http://nephron.org/cgi-bin/MDRD_GFR/cgi)

CABG = Coronary artery bypass graft surgery; PCI = Percutaneous coronary intervention; HbA1c = Glycated hemoglobin; RS = Rating Scale; PGWB = Psychological General Well-being index

died and of those 58 (82%) by CV reasons. The event rates were similar between genders. The impact of a decrease in RS and PGWB scores on subsequent CV events and mortality are shown in Table 4. The median RS score was lower among male patients experiencing CV event or death than among their event-free counterparts. No such associations were observed in women (Figure 8). Mortality in relation to RS scores above and below median and gender specific distribution are shown in Figure 9. Age and chronic heart failure were independent predictors of mortality in both genders. Previous MI and creatinine clearance predicted mortality in men while a high body mass index (BMI) was predictive in women. Previous MI and chronic heart failure were predictors of CV events in both genders while age and creatinine clearance predicted CV events only in men.

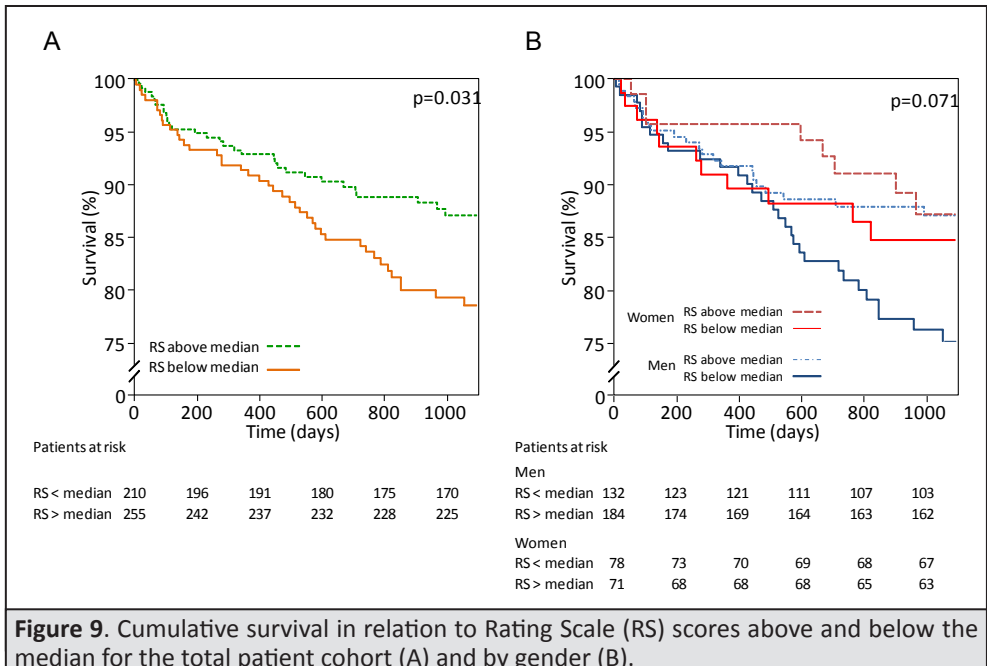
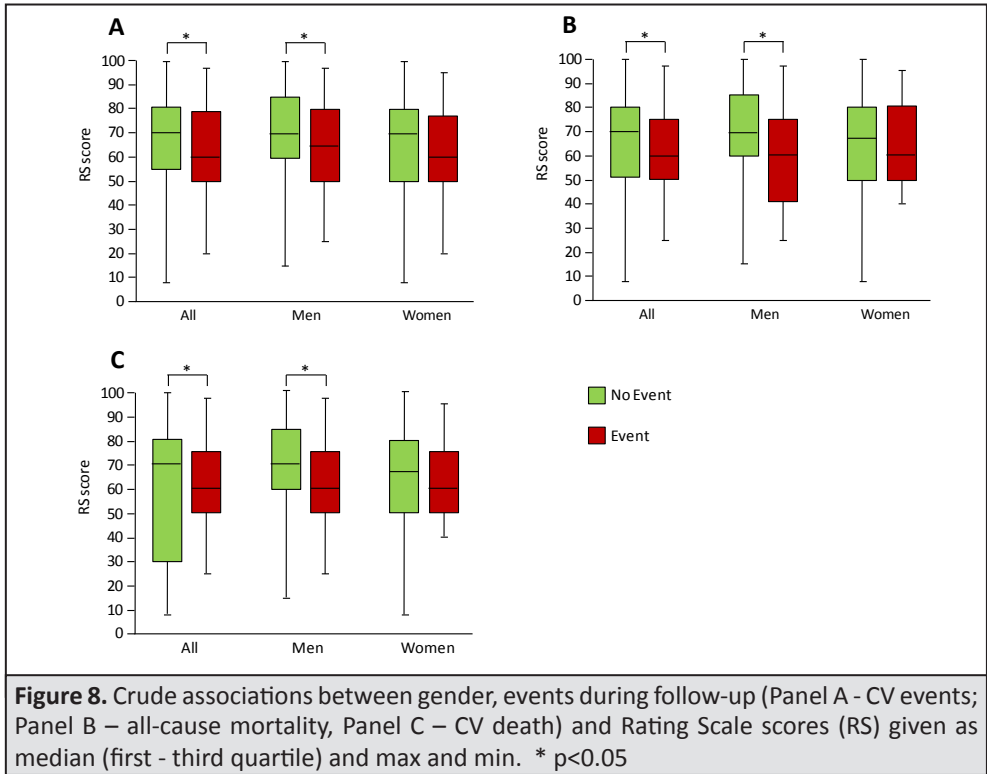
**Table 4.** Crude and adjusted prospective associations between Rating Scale scores (RS), Psychological General Well-being index (PGWB) scores and cardiovascular events (CVE), all-cause mortality and cardiovascular (CV) death given as hazard ratios (HR) with 95% confidence intervals (95% CI).

	HR	95%CI	p-value
<b>RS (per 10 unit decrease)</b>			
<i>CVE (fatal and nonfatal myocardial infarction or stroke)</i>			
Unadjusted (n=465; CVE=132)	0.87	0.80-0.95	0.002
Adjusted for risk factors*	0.90	0.83-0.99	0.028
Men (n=316; CVE=86)	0.86	0.77-0.97	0.010
Women (n= 149, CVE=46)	0.98	0.84-1.14	0.791
<i>All-cause mortality</i>			
Unadjusted (n=465;deaths=71)	0.86	0.76-0.97	0.012
Adjusted for risk factors†	0.90	0.79-1.02	0.101
Men (n=316; deaths=52)	0.85	0.73-0.99	0.038
Women (n=149; deaths=19)	1.01	0.77-1.33	0.932
<i>CV death</i>			
Unadjusted (n=465;CV deaths=58)	0.86	0.76-0.98	0.027
Adjusted for risk factors†	0.90	0.78-1.04	0.160
Men (n=316; CV deaths=43)	0.88	0.74-1.04	0.128
Women (n=149; CV deaths=15)	0.95	0.70-1.30	0.763
<b>PGWB (per 10 unit decrease)</b>			
<i>CVE (fatal and nonfatal myocardial infarction or stroke)</i>			
Unadjusted (n=465; CVE=132)	0.97	0.85-1.11	0.696
Adjusted for risk factors*	1.02	0.89-1.16	0.781
Men (n=316; CVE=86)	0.97	0.83-1.14	0.721
Women (n= 149, CVE=46)	1.06	0.83-1.36	0.637
<i>All-cause mortality</i>			
Unadjusted (n=465;deaths=71)	0.98	0.83-1.17	0.846
Adjusted for risk factors†	1.05	0.89-1.24	0.552
Men (n=316; deaths=52)	1.01	0.84-1.22	0.912
Women (n=149; deaths=19)	1.07	0.79-1.46	0.666
<i>CV death</i>			
Unadjusted (n=465;CV deaths=58)	1.02	0.83-1.26	0.850
Adjusted for risk factors†	1.09	0.89-1.33	0.424
Men (n=316; CV deaths=43)	1.12	0.85-1.47	0.422
Women (n=149; CV deaths=15)	0.98	0.74-1.29	0.863

\*Age, previous myocardial infarction, congestive heart failure, creatinine clearance;

† Age, BMI, previous myocardial infarction, congestive heart failure, creatinine clearance;

BMI = Body mass index



## Study III

### Patient characteristics

Three hundred and twenty four patients in the QoL substudy completed DTSQ, PGWB and RS both at baseline and at the 12-month follow-up visit. Sixty one percent of these patients were treated with insulin while the rest were prescribed oral glucose lowering agents. Baseline characteristics of the present population are presented in Table 5. In insulin-treated patients the diabetes duration was longer, HbA1c higher and history of hyperlipidemia, hypertension, previous MI, previous heart failure and CABG more prevalent than among those prescribed oral glucose lowering agents.

### Quality of life

Treatment satisfaction (DTSQ) and psychological well-being (PGWB), that were similar between the treatment groups at baseline, improved significantly during the follow-up in

**Table 5.** Baseline characteristics in Study III. Data are expressed as median (first-third quartile) or number (%)

Variable	All n=324	Insulin n=197	Oral n=127	p-value
Age (years)	67 (59-73)	67 (59-73)	67 (58-73)	0.914
Male gender	229 (71)	98 (77)	131 (67)	0.040
Diabetes duration (years)	5 (2-12)	8 (4-15)	3 (0-18)	<0.001
Body mass index (kg/m <sup>2</sup> )	28 (26-31)	28 (26-31)	28 (26-31)	1.000
Smokers	83 (26)	45 (22)	38 (30)	0.163
History of				
Myocardial infarction	114 (35)	82 (41)	32 (25)	0.003
Heart failure	57 (18)	47 (24)	10 (8)	<0.001
Hypertension	159 (49)	109 (55)	50 (39)	0.005
CABG	46 (14)	37 (19)	9 (7)	0.003
PCI	34 (10)	24 (12)	10 (8)	0.217
Hyperlipidemia	97 (30)	70 (36)	27 (21)	0.006
Biochemistry				
HbA1c (%)*	7.2 (6.3-8.5)	7.6 (6.5-8.7)	6.7 (5.9-7.9)	<0.001
B-glucose (mmol/L)	12.1 (9.6-14.9)	12.3 (9.6-15.4)	12.0 (9.6-14.2)	0.374
Creatinine clearance (ml/min) <sup>†</sup>	75 (54-97)	73 (52-97)	76 (58-92)	0.706
Cholesterol (mmol/L)	5.1 (4.3-6.0)	5.0 (4.7-5.9)	5.3 (4.5-6.2)	0.027
Triglycerides (mmol/L)	1.8 (1.2-2.8)	1.7 (1.2-2.6)	1.8 (1.3-2.9)	0.519

\* DCCT (Diabetes Control and Complications Trial) HbA1c targets of 6.5% -7.5%

<sup>†</sup> Glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault calculator available at [http://nephron.org/cgi-bin/MDRD\\_GFR/cgi](http://nephron.org/cgi-bin/MDRD_GFR/cgi)

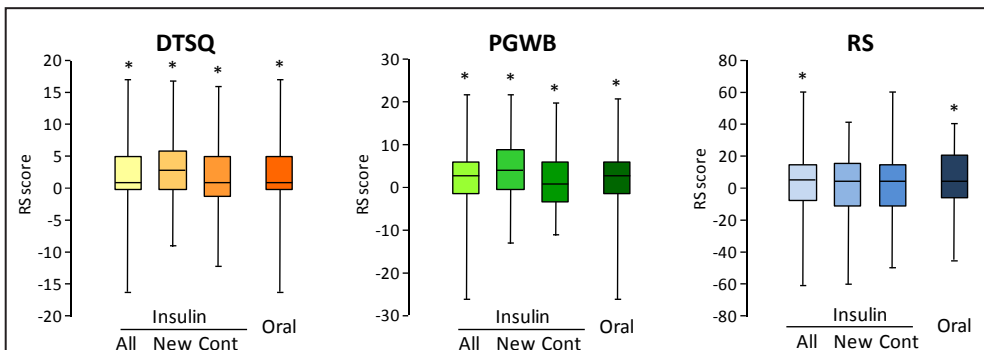
CABG = Coronary artery bypass graft surgery; PCI = Percutaneous coronary intervention; HbA1c = Glycated hemoglobin

both groups and did not differ between the treatment groups at 12 months (Table 6 and Figure 10). Self-perceived health (RS) was lower in patients treated with insulin compared with patients on oral treatment both at baseline and after 12 months. It did, however, improve significantly in both groups over time. At 12 months patients with newly introduced insulin rated similar treatment satisfaction and perceived health but higher psychological well-being compared with patients who continued previously instituted insulin (Table 6).

**Table 6.** Comparisons of QoL scores at baseline and 12 months by treatment group. Data are expressed as median (first-third quartile)

Questionnaire	Insulin	Oral	p-value	Insulin		p-value
				New	Continued	
<b>DTSQ</b>	n=134	n=58		n=47	n=87	
Baseline	30 (24-34)	31 (27-34)	0.197	31 (25-34)	30 (23-34)	0.634
12 months	n=146	n=70		n=62	n=84	
	32 (28-35)	34 (30-36)	0.149	34 (28-36)	31 (27-35)	0.059
<b>PGWB</b>	n=191	n=123		n=91	n=100	
Baseline	77 (73-82)	79 (76-82)	0.163	77 (72-81)	78 (74-83)	0.348
12 months	81(78-84)	82 (78-84)	0.735	82 (79-85)	81 (77-83)	0.038
<b>RS</b>	n=158	n=112		n=74	n=84	
Baseline	70 (50-80)	75 (60-85)	0.030	70 (50-80)	69 (50-80)	0.476
12 months	70 (57-85)	80 (70-90)	0.001	72 (58-85)	70 (56-84)	0.561

DTSQ = Diabetes Treatment Satisfaction Questionnaire; PGWB = Psychological General Well-being index; RS = Rating Scale



**Figure 10.** Change in QoL scores according the type of glucose lowering treatment. Data are presented as delta values (median and first-third quartile) between those achieved at baseline and after 12 months of follow up. DTSQ = Diabetes Treatment Satisfaction Questionnaire; PGWB = Psychological General Well-being index; RS = Rating Scale score; Cont = Continued; \* p<0.05

### *Quality of life in relation to glycemic control*

HbA1c was higher in insulin treated patients compared to patients using oral glucose lowering agents both at baseline (median (first-third quartile) 7.6 (6.5-8.7) vs. 6.7 (5.9-7.9),  $p=0.001$ ) and at 12 months (6.8 (6.1-7.9) vs. 6.2 (5.5-7.2),  $p<0.001$ ). A decrease in HbA1c over time was noticed in 50% of the patients with a similar magnitude between the groups. Decrease in HbA1c over time was associated with improvement in all QoL measures while increased or stable HbA1c was associated with improved PGWB only (Figure 11A).

Self-reported hypoglycemic episodes were more frequent in patients using insulin than among those with oral glucose lowering treatment (at baseline  $n=67$  (50%) vs.  $n=16$  (30%),  $p=0.004$ ; and at 12 months ( $n=81$  (52%) vs.  $n=23$  (30%),  $p=0.002$ ), and was associated with lower treatment satisfaction (Figure 11B).

### *Quality of life and gender*

Treatment satisfaction and psychological well-being was higher in men than women at baseline and men also reported higher psychological well-being at 12 months (Figure 11C). Both genders improved treatment satisfaction and psychological well-being significantly over time while self-rated health only improved in men.

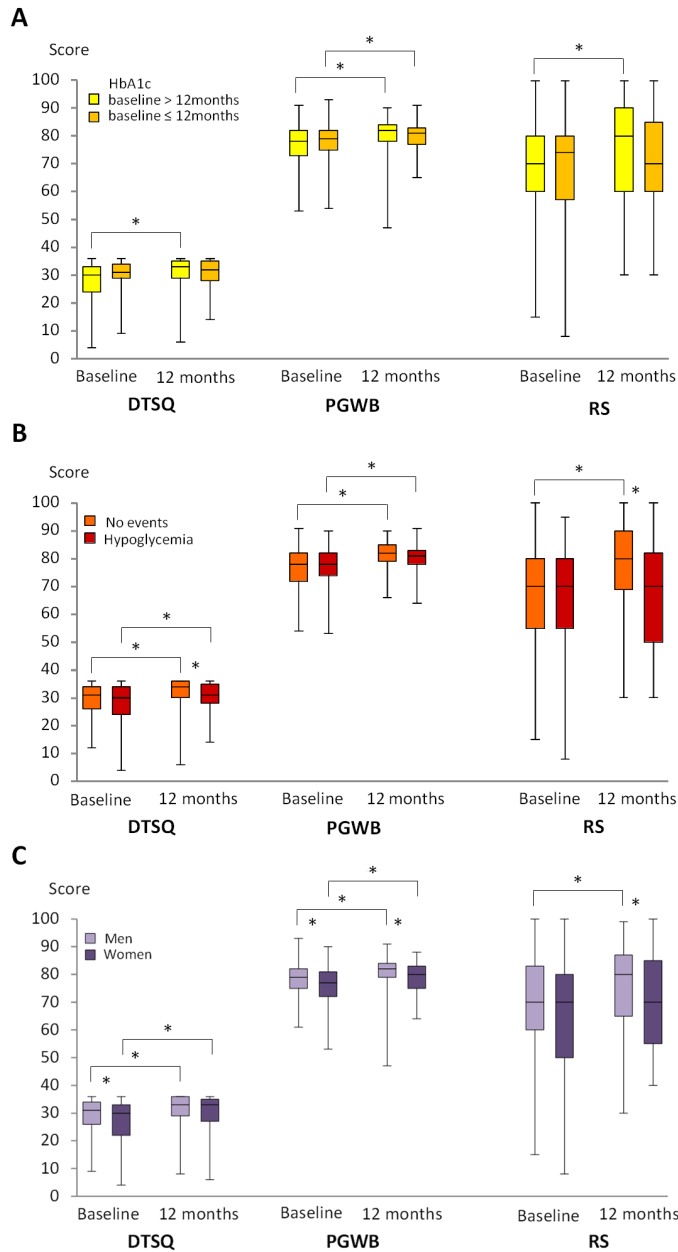
## **Study IV**

### *Patient characteristics*

Pertinent characteristics of 73 patients (33 original DADD participants (Group 1) and 40 subjects not considered eligible for DADD during the screening (Group 2)) are presented in Table 7. At the time for DADD-FU patients in Group 1 were older, had developed more hypertension, had higher BMI, systolic blood pressure, HbA1c and S-creatinine but lower cholesterol and low-density lipoprotein levels and they were more often prescribed angiotensin converting enzyme inhibitors compared to baseline. Patients in Group 2 were older and had higher HbA1c. LV systolic function remained normal in all patients (WMI  $1.0 \pm 0$ ) over time.

### *Echo-Doppler and tissue Doppler imaging data*

The E/A ratio decreased significantly over time in both Group 1 and 2 (Table 8a and 8b) while the E/e' ratio decreased significantly only in Group 1. In Group 1 measures of diastolic function normalized in 16 (48%) and remained unchanged in 17 (52%). E/A ratio was higher in patients who normalised LV diastolic function compared with patients in whom LVDD remained stable (baseline  $1.1 \pm 0.3$  vs.  $0.9 \pm 0.3$ ,  $p=0.020$ , follow-up  $1.0 \pm 0.2$  vs.  $0.8 \pm 0.3$ ,  $p=0.002$ ). In Group 2, 35 patients had a normal diastolic function at baseline and eight of them (23%) developed LVDD over time. Of the five patients in Group 2 with LVDD at baseline diastolic function returned to normal in four. At the time of follow-up in Group 2 the E/A ratio was higher in patients with remaining normal LV diastolic function compared to patients who developed LVDD ( $1.0 \pm 0.2$  vs.  $0.8 \pm 0.3$ ,  $p=0.001$ ). There was no difference in LV diastolic function (E/A, E/e') between genders at baseline or at follow-up in either of the two groups. Myocardial blood volume index, available from 22 patients in Group 1, did not change over time.



**Figure 11.** QoL scores at baseline and after 12 months of follow up by change in HbA1c (A), self-reported hypoglycemia (B) and gender (C). Data are expressed as median (first-third quartile).

HbA1c baseline >12 months = HbA1c lower at 12 months; HbA1c baseline ≤12 months = HbA1c unchanged or increased 12 months; DTSQ = Diabetes Treatment Satisfaction Questionnaire; PGWB = Psychological General Well-being index; RS = Rating Scale score;

\*  $p < 0.05$

**Table 7.** Patient characteristics in Group 1 (n=33) and Group 2 (n=40) in Study IV. Data are expressed as mean±SD or number (%)

Variables	DADD	DADD-FU	p-value
<b>Group 1</b>			
Age (years)	61±7	67±7	<0.001
Male gender	12 (36)	12 (36)	NA
Diabetes duration (years)	6±4	12±6	<0.001
Body mass index (kg/m <sup>2</sup> )	28±5	29±6	0.013
Blood pressure (mmHg)			
Systolic	143±17	153±14	0.014
Diastolic	80±7	82±9	0.215
Treated hypertension	14 (42)	24 (73)	0.001
Current smokers	3 (9)	3(9)	1.000
<i>Cardiovascular treatment</i>			
β-blockers	7 (21)	8 (24)	0.572
ACE-i/ARB	11 (33)	18 (55)	0.017
Calcium antagonists	5 (15)	8 (24)	0.083
Diuretics	8 (24)	11 (33)	0.263
ASA	7 (21)	11 (34)	0.057
Statins	10 (30)	17 (53)	0.057
<i>Glucose lowering treatment</i>			
Metformin	19 (58)	21 (64)	0.488
Glitazon	0	1 (3)	0.325
Repaglinide	7 (21)	6 (18)	0.712
Other oral*	0	3 (9)	0.083
Insulin	17(52)	14 (42)	0.184
<i>Laboratory tests</i>			
FPG (mmol/L)	6.5±3.3	7.2±1.7	0.350
HbA1c (%)	5.4±1.4	6.2±4.8	0.002
S-creatinine (mmol/L)	68±11	71±51	0.031
NT-proBNP (ng/L)	80±96	69±51	0.309
Cholesterol (mmol/L)	5.0±1.0	4.4±0.9	0.002
HDL (mmol/L)	1.4±0.6	1.2±0.4	0.078
LDL (mmol/L)	3.0±0.9	2.6±0.8	0.011
Triglycerides (mmol/L)	1.4±1.0	1.2±0.7	0.548
<b>Group 2</b>			
Age (years)	59±7	66±7	<0.001
Male gender	24 (60)	24 (60)	NA
Diabetes duration (years)	5±4	12±4	<0.001
Body mass index (kg/m <sup>2</sup> )	27±4	28±4	0.522
<i>Laboratory tests</i>			
FPG (mmol/L)	7.5±1.6	8.0±2.9	0.204
HbA1c (%)	5.8±0.9	6.3±1.3	0.018
S-creatinine (mmol/L)	76±12	72±15	0.069

ACE-I = Angiotensin-converting-enzyme inhibitor; ARB = Angiotensin receptor blockers; ASA = Aspirin (acetylsalicylic acid); FPG = Fasting plasma glucose; HbA1c = Glycated hemoglobin; NT-proBNP = N-terminal pro hormone of brain natriuretic peptide; \*Other oral = Sulfonylurea, sitagliptin; HDL= High-density lipoprotein; LDL= Low-density lipoprotein; NA = not applicable

**Table 8 a and b.** Echocardiographic measurements in Group 1 (n=33; a) and Group 2 (n=40; b). Data are presented as mean±SD

Variables	DADD	DADD-FU	p-value
E (cm/s)	71±15	70±16	0.872
A (cm/s)	76±17	82±17	0.002
E/A	1.0±0.3	0.9±0.3	0.003
e' (cm/s)	8.3±1.3	11.0± 2.7	<0.001
E/e'	8.7±2.0	6.7± 2.0	<0.001
LAVI (ml/m <sup>2</sup> )	31±6	22±5	<0.001

LAVI = Left atrium volume index

Variables	DADD	DADD-FU	p-value
E (cm/s)	72±14	69± 13	0.154
A (cm/s)	66±14	75±12	<0.001
E/A	1.1±0.3	1.0±0.2	<0.001
e' (cm/s)	10.4±1.7	11.0±2.1	0.221
E/e'	7.0±1.6	6.4± 1.7	0.060

# GENERAL DISCUSSION

Over the last decades there has been a substantial decline in the age-standardized mortality in the general population (109-112) due to improved treatment strategies and a reduction of classical risk factors (113; 114). Also patients with diabetes have experienced decreasing mortality although it remains considerably higher than among their counterparts without diabetes (115-117). As an example, one year mortality in Swedish patients with MI without diabetes was 16.5% in 1995 decreasing to 6.5% in 2010, which should be compared with 30% and 15% respectively in patients with diabetes (118). The clustering of metabolic risk factors in people with diabetes may be one explanation and the direct effects of hyperglycemia on the vasculature another. A less than optimal management of this patient category has also been indicated as a factor to consider (42; 119). Although a combination of diet and oral glucose lowering agents is sufficient for the initial control of hyperglycemia, glucose levels are known to gradually rise with the progression of the disease increasing the proportion of patients in need of insulin therapy. The institution of an insulin-based glucose control is, however, frequently delayed and one reason may be that it has been linked to a decreased QoL (67). An improved glycemic control may, on the other hand, favorably influence the subjective feeling of well-being due to decreased prevalence of long-term complications. The impact of different glucose-lowering strategies on QoL is not well explored and further investigations are warranted. Understanding diabetes related complications is also necessary to acquire knowledge needed to improve the management of this expanding patient population. The contribution of diabetes to vascular disease has been the subject of rather extensive research while early signs of diabetes related myocardial dysfunction needs more attention. The studies of the present thesis focused on factors which may be of a prognostic importance and thereby of potential therapeutic implications in patients with diabetes and CVD; gender, QoL and LV myocardial diastolic function.

## Gender and survival

The findings of Study I demonstrate a relatively higher risk for subsequent CV event in women with diabetes surviving acute MI compared with men. This increased risk may relate to a higher risk factor burden rather than gender.

Diabetes is considered an independent risk factor for CAD and mortality in the elderly and in women of all age groups (87; 120-122). This raises the question whether women are exposed to unique risk factors or if they, in the presence of diabetes, lack protective factors that otherwise are present. Gender-specific analyses in a patient population with diabetes and MI should have the capacity to bring further information on this issue since it comprises subjects at an increased risk for future CV events. Study I was performed in an attempt to add information about the joined effects of diabetes and an acute MI separately in men and women. Due to a high, protocol defined use of evidence-based pharmacological therapy, revascularizations and a reasonable glucose control of a similar magnitude in both genders the DIGAMI 2 population is well suited for this purpose. Comparing events between women and men, the former group ran an increased risk of the combined endpoint of CV mortality and morbidity over time. This increased risk related to age and could not be explained by

gender in itself. Such findings warrant the assumption that mortality will not differ between the two genders if they are subjected to a carefully conducted evidence-based management. Moreover Study I did not support previous observations that the youngest women have an especially high mortality and morbidity risk compared with those that are older (86; 123). One explanation to these contradictory findings could be that DIGAMI 2 only recruited patients with type 2 diabetes. The increased mortality risk in younger patients seen in previous registry based reports, in which the type of diabetes could not be verified, may relate to the presence of patients with type 1 diabetes with more advanced co-morbidity. The contrast between the present and previous findings warrants further investigations.

In general, the risk factors behind CVD are similar in men and women. It has, however, been speculated that the presence of diabetes may cause gender related differences in the risk factor pattern or lead to a more dismal effect in women (89). Factors as hypertension and dyslipidemia has been shown as more prevalent in women with diabetes (124) and associated with an excessive risk of CV morbidity and mortality compared to men (89; 125). In Study I, the female patients had a more advanced CVD already at hospital admission for MI. This was reflected by their higher prevalence of hypertension, heart failure, higher cholesterol and that they more frequently were prescribed diuretics. Their lower use of aspirin and the similarity in the use of beta-blockers and ACE inhibitors between men and women at admission contrasts the higher risk factor burden among the female patients indicating suboptimal treatment. The present findings enhances the importance of previous observations that substantially higher diabetes associated risk in women with diabetes compared to men is due to a more pronounced CV risk factor profile in the former already at the time of a coronary event (123; 126; 127).

In Study I blood glucose at randomisation was an independent prognostic predictor in men, however, not in women despite a similar glycemic control between the two genders. It may be speculated that women are more influenced by their heavier risk factor profile when they get their MI than by the subsequent glucose control. Accordingly, adequate glucose control needs to be initiated earlier, even prior to the development of CV events, in order to be effective. This assumption gain some support from the long term follow up of UKPDS (128). Strength of the present analysis is that Study I is based on a cohort of extremely well-characterized MI patients with type 2 diabetes allowing adjustments for diabetes related factors ordinarily not well described in MI trials. However, the outcome is limited to the patients included in the DIGAMI 2 trial and caution should therefore be used before generalizing to other patient categories with diabetes and CVD.

In conclusion, the increased risk of fatal and non-fatal CV events in women with diabetes and MI predominantly relates to their higher age and prevalence of concomitant diseases but not to gender per se. Multifactorial risk reduction strategies applied at an early stage of CVD may possibly improve their future prognosis.

### **Risk Assessment in patients with diabetes**

The findings of Study II illustrate that in patients with type 2 diabetes and acute MI self-rated health measured by RS identify those at increased risk for subsequent CV morbidity and death from any cause.

Randomized trials have demonstrated that reduction of diabetes related complications is possible (129-132). Thus, identification of patients at high risk for CV events is important in

order to achieve treatment goals and modify the prognosis. Patients with diabetes are often simply referred to as high-risk individuals e.g. in the European guidelines for CVD prevention (133). Still, several attempts have been made to develop more precise risk engines for this patient category. The accuracy of these risk predicting tools have been questioned since they are based on patient populations recruited at a time when management differed from that presently practiced (134-138). The most recent model, based on the large and comprehensive Swedish diabetes registry, took the following variables into account: age, diabetes duration, total-cholesterol-to-HDL-cholesterol ratio, HbA1c, blood pressure, BMI, gender, smoking habits, albuminuria, atrial fibrillation and previous CVD to elaborate an equation for the five year risk for CVD (139). None of the risk engines has, however, included any measure of the patient's opinion on their self-rated health or QoL. The objective of Study II was to see whether such information may be worthwhile to include as a risk estimate among other disease related variables.

For the purpose of Study II, investigating the predictive value of self-perceived QoL, generic rather than disease-specific tools were applied. The RS was selected as a simple, validated tool to quantify a general feeling of health (101). Evaluated by one global question such as "How do you define your current health?" it provided a description of the self-perceived health status comprising not only physical but also psychological, emotional and social dimensions. It has been claimed that single-item tools are valid and reliable (140; 141), but it has also been suggested that they lack precision when assessing health-related QoL (142). However, the simplicity of single-item tools makes them highly feasible in a clinical setting when dealing with patients with acute illnesses. The association between self-rated health and health outcomes such as CV events (143) and mortality (144; 145) is well established in patients of different ages in various populations (146) and in a variety of diseases (68; 70; 74; 147) including diabetes (71; 72; 148; 149) and MI (150). The associations between poor mental health and increase in mortality have also been described in patients with diabetes (151; 152). However, such associations were, at least until now, less well explored in patients with both type 2 diabetes and MI. To test the hypothesis in Study II the PGWB was chosen as a valid measure of mental health since it has been tested in patients with type 2 diabetes (100) and considered appropriate for measuring psychological well-being (153) in this patient group. The findings of Study II illustrate that, after controlling for potential confounders such as age, previous MI, heart failure and creatinine clearance, there was a relationship between the RS scores and CV events and mortality in patients with type 2 diabetes surviving MI. In the gender specific analysis the association was statistically significant in men but not in women. A general pattern in health-related QoL studies is that women rate their perceived health lower than men. This is seen across different age groups and in a number of clinical conditions (154; 155). A less favourable rating of health in women seems to lack prognostic value in contrast to the impact of a low self-reported health in men. Men tend to report fewer but more disease-specific symptoms while women are more likely to take less disease-relevant conditions, among them needs, priorities and social function, into account (156; 157). It should also be noted that a relatively low proportion of women in the present cohort increases the possibility of a type 2 statistical error. No relation between psychological general well-being and survival was found in Study II. This could possibly be explained by that PGWB scores in the present cohort were similar compared to the scores reported by the age matched peers in a general population (158) and that it did not differ between genders. Moreover diabetes has been reported to affect physical well-being more than psychological (100; 159).

In conclusion, the present study suggests that the RS is an easy-to-use, low-cost and time-efficient tool, which could help to identify patients with diabetes and MI at risk for subsequent CVD. This association appears stronger in men than women but further studies in larger patient cohorts are needed to verify a true gender related difference. Introduced in routine clinical practice the easily applied RS score may improve identification of patients at risk and subsequent decision-making.

## **Glucose lowering treatment and QoL**

The main finding in Study III was that an insulin based glucose lowering treatment was well accepted without any negative impact on treatment satisfaction or psychological well-being compared to oral glucose lowering treatment in patients with type 2 diabetes and MI. Moreover improved glycemic control had a favourable effect on QoL.

The risk of CV morbidity and mortality increases with increasing hyperglycemia (160; 161). Careful risk factor management, including an adequate glucose control (162), are essential components in the attempts to postpone progression of CV complications and to improve survival in patients with type 2 diabetes. The impact of oral glucose lowering agents often becomes insufficient over time leading to a demand for insulin to keep HbA1c at a reasonable level. Despite existing evidence and management recommendations (163) many patients do not receive care according to current standards of practice (164; 165). A large prospective, population-based study using data of 7,208 patients treated with oral glucose lowering drugs indicated that by the time insulin therapy was initiated, the average patient had lived nearly five years with a HbA1c >8% and about ten years with a HbA1c >7% (166). The reluctance of physicians to initiate insulin may be based on some objective but also many perceived barriers. These include potential negative effects on QoL, concerns about complexity of treatment regimens, needle anxiety and treatment side effects, mostly hypoglycemia and weight gain (167-169). However, neither of the “physical” concerns turned out to be of any major importance in the recently published ORIGIN trial (170). The results of this study demonstrated only a modest increase in weight and hypoglycemic episodes in patients treated with insulin. Decrease in QoL and low satisfaction with treatment is indeed a relevant issue not only from a psychological perspective, but also because it affects adherence to the prescribed glucose lowering treatment (171; 172). A better understanding of this problem could support an earlier institution of insulin based glucose lowering therapy when needed.

A number of former studies investigating the effects of insulin on satisfaction with treatment in patients with type 2 diabetes showed both negative (77; 172; 173) and positive (174-176) effects of such therapy. Interestingly, it was studies based on a single observation that showed worse satisfaction with treatment in patients on insulin compared to oral glucose lowering treatment (77; 172; 173) while longitudinal studies in populations treated with insulin demonstrated improved treatment satisfaction over time (174-176). Patients with poorly managed diabetes may have barriers to insulin treatment, but once insulin is initiated, the therapy may be experienced as beneficial (177) due to the improvement in glycemic control (172). Moreover, an easy access to care and good communication between the patient and health care provider may add to treatment satisfaction (178-180). In Study III we found that insulin therapy, newly instituted or continued, was associated with improved treatment satisfaction and psychological well-being over time in patients with type 2 diabetes and MI.

There was no difference in satisfaction with treatment or psychological well-being between patients treated with insulin or oral glucose lowering agents at the start of the study. Moreover, satisfaction with treatment improved in both groups over time. One may speculate that the higher baseline HbA1c in the insulin group, above the recommended target, contributed to an impression of disease severity. Thus, as HbA1c decreased, treatment satisfaction increased. It has been suggested that treatment satisfaction is mediated by perceived benefits while treatment preferences relate more to side effects (181). The significant increase in the QoL measures for patients with decreasing HbA1c supports the hypothesis that a negative attitude toward insulin injections may be counterbalanced by an improved glycemic control. Patients with hypoglycemic episodes reported a lower treatment satisfaction compared to those without, which is in line with this assumption and previous reports (182). An alternate explanation for the improved satisfaction with treatment is that our patients, all included in a clinical trial, were treated by specialists in a hospital setting and provided with ample time and attention. As already indicated, impaired treatment satisfaction and compromised psychological status are considered to be associated with less efficient self-care and low adherence to prescribed therapy (183). The present findings of similar treatment satisfaction and well-being in patients prescribed insulin and oral glucose lowering agents should encourage to earlier institution of insulin when needed.

In conclusion there was no difference in treatment satisfaction and psychological well-being between patients allocated to different glucose lowering treatments. Results from Study III suggest that treatment with insulin is well accepted and that it may be associated with improved glycemic control which may offset potentially unfavorable aspects of insulin self-administration.

## **Diabetes and LVDD**

The main finding of the study IV was that LVDD remained unchanged or normalized in a majority of patients with type 2 diabetes and no clinical signs of CVD over a period of six years.

LVDD defined as abnormalities in the relaxation, filling and distensibility of the LV (184) may exist in patients with type 2 diabetes regardless of clinically detectable CVD. A disturbed diastolic relaxation of the LV may indeed be detectable as soon as a few years after diabetes has been diagnosed (185). It has been suggested that LVDD deteriorates over time and that it may contribute to the development of clinically overt heart failure. However, data on the natural course of LV diastolic function in patients with diabetes is sparse and the relationship between LVDD and heart failure is a matter of debate. The objective of Study IV was to investigate the progress of LV diastolic function and myocardial blood flow reserve over time in patients with type 2 diabetes free from clinically detectable CVD.

Study IV confirmed the existence of LVDD in patients with type 2 diabetes without any evidence of structural heart disease. However, the prevalence of 52% at baseline and 36% at follow-up was lower than the 46-75 % described in previous reports (60-62). One explanation may be that methods for the diagnosis of LVDD differ between studies. The LV diastolic function in Study IV was evaluated by a stepwise approach incorporating data from the analyses of the mitral inflow velocity curves, TDI of mitral annular motion and

LA volume index. The diagnosis of LVDD was based on the criteria suggested by the Mayo Clinic at the time of original DADD study, which are somewhat different from the current recommendations (55). In DADD-FU, as in DADD, the presence of LVDD was based on the detection of at least one criterion. If the diagnosis had been based on two or more criteria the prevalence of LVDD had been even lower favoring the assumption that the prevalence may be rather low in a middle age patients with diabetes without symptoms or signs of CVD.

A population-based study examining longitudinal effects of diabetes on LV diastolic function (185) demonstrated an association between diabetes duration of four years or more and the presence of LVDD. However, this study included patients with both type 1 and 2 diabetes and did not screen for CAD and valvular disease in order to reveal other potential contributors to LVDD. A deterioration of LV diastolic function over a follow-up period of similar length was also demonstrated in a cohort of subjects from the general population, including apparently healthy subjects (186), a finding that may be explained by the effects of aging. The prevalence of LVDD is hard to compare between studies partially due to different diagnostic definitions of LVDD and/or concomitant presence of CVD, even if minor, in the investigated population. Among known confounders myocardial ischemia, LV hypertrophy due to hypertension and valvular heart disease are the most common and important. Patients with any signs of such disease were excluded from Study IV. If present, hypertension was mild and well controlled and the glycemic status well balanced. These factors may have been of relevance for the positive findings as regards myocardial performance. Still studies like Study IV are sparse and the common assumption that diabetes necessarily causes a progressive deterioration of LV diastolic function may be questioned, encouraging to further efforts to explore the true longitudinal impact of hyperglycaemic conditions on myocardial performance.

In conclusion, LV diastolic function remained stable or even improved in a majority of the investigated patients with type 2 diabetes and no apparent CVD over an observation period of six years while only a small proportion of patients with normal LV diastolic function at baseline developed signs of LVDD. One may speculate that glucose lowering treatment together with carefully managed CV risk factors contributed to this finding.

### **Future implications**

A majority of subjects with diabetes mellitus have an unfavorable CV prognosis. Recognition of the extent to which diabetes specific risk factors contributes to CVD may help to improve prognosis in such patients. The present thesis discusses some aspects that may be involved in the development and progression of CAD and myocardial dysfunction in patients with type 2 diabetes. Furthermore, it suggests ways to identify patients at increased risk for CV morbidity and mortality.

The presence of diabetes and established CAD attenuates the advantage of being a woman equalizing the risk for subsequent CV events and mortality between the genders. A more advanced risk factor profile observed in women with type 2 diabetes compared with men may partly explain the excess in their CV risk. Thus, one can speculate that increased attention to primary prevention of CVD in women with diabetes may improve their outcome. Efficient application of preventive strategies requires an accurate risk assessment that helps to identify individuals at high risk for unfavorable outcomes and intensify their treatment. However, simple and updated risk assessment tools are sparse. Prognostic implications of self-rated

health observed among patients with type 2 diabetes and established CVD should encourage the incorporation of such, an easy to administer, risk assessment method in future risk engines. Integrated into clinical practice it may help to determine the most vulnerable individuals which would benefit from more intensive therapeutic interventions. Although insulin is the most potent and reliable glucose lowering agent, its use is often postponed due to the barriers perceived by patients and health-care providers. The findings of present thesis suggest that insulin-based glucose-lowering treatment is well accepted and should not be reserved as a last resort after other diabetes treatment strategies have failed. Diabetes induced metabolic perturbations have a significant negative impact on the structural and functional changes in myocardium. Contrary to the common believe that such changes gradually deteriorate leading to the development of heart failure the present thesis demonstrate that myocardial function may remain stable or even improve over the time. An increased attention should be paid to the achievement of glycemic goals in patients with type 2 diabetes. Maintenance of optimal glycemic control may not only reduce morbidity and mortality but also contribute to a positive long-term effect on the QoL.

# CONCLUSIONS

1. Increased risk of fatal and nonfatal cardiovascular events in women with type 2 diabetes and myocardial infarction compared to men may be explained by older age and a more advance risk factor profile.
2. A low self-rated health may identify male patients with type 2 diabetes and acute myocardial infarction at increased risk for all-cause mortality or cardiovascular events.
3. Insulin-based therapy is well accepted and does not decrease treatment satisfaction and psychological well-being compared to oral glucose lowering treatment in patients with type 2 diabetes and myocardial infarction.
4. Left ventricular diastolic function improved or remained stable in a majority of the investigated patients with type 2 diabetes and no apparent cardiovascular disease over an observation period of six years.

# ACKNOWLEDGEMENTS

The best and worst moments of my dissertation journey have been affected, influenced or shared with many remarkable people.

First and foremost I would like to express my sincerest gratitude to my main supervisor Barbro Kjellström for her guidance, infinite support, enlightening discussions and capacity to combine critique and encouragement in times of new ideas and difficulties. Thank you for a great deal of patience allowing me the freedom to work in my own way as well as your thoughtful input and sharp editing which have been invaluable to the completion of this thesis.

I am also greatly indebted to Professor Emeritus Lars Rydén, my co-supervisor, who truly made a difference in my life and has always been and continues to be a constant source of inspiration and insight. I will forever be grateful for all your care, wisdom and tireless assistance. Without your support I would not have been able to do what I have done and become who I am.

I owe sincere and earnest thankfulness to my co-supervisor Christina Jarnert for her help, encouragement, excellent advices and positive attitude despite the situation.

I am thankful to my co-supervisor John Öhrvik for the statistical support, guidance and hours of discussions spent during the interpretation of the data.

To Mai-Lis Hellénus, my mentor, whose support and friendship has been invaluable.

To my co-authors, Professor Kerstin Brismar and Tina Rydén-Bergsten, for the guidance and constructive feedback.

To Professor Jolanta Vaškelytė for being a source of inspiration, a teacher and a role model during my early days of studies.

To my wonderful colleagues and roommates Anna Norhammar, Linda Garcia Mellbin and Isabelle Johansson, for they steady support and understanding during the write-up stage.

To Camilla Hage for proofreading *all* of my thesis and providing me with numerous advices.

To Eva Wallgren for helping me enormously doing the final formatting of the thesis.

Many thanks to Raquel Binisi for the support and friendship which have made the research department more than a place for studies for me and many other PhD students from all around the world.

Thanks to the members of Diabetes and Cardiovascular Diseases research team Ann Lindström, Victoria Boström and Matthias Lidin who worked for the success of the DADD follow-up study assisting with the collection of data and all the patients who participated.

To staff in the research department - thank you for welcoming me and helping to develop the ideas in this thesis.

I am grateful to Mark Ryden, a great artist, fulfilling my dream and letting me use his artwork for the cover of my thesis.

Thanks to:

My friends Vilija Okė and Mantas Okas, graduated PhD students, for the inspiration and helping me to find a place where I belong. You are one of the most dedicated people in work and research and the most “alive” I’ve ever known.

Ivana Girdzijauskas and Šarūnas Girdzijauskas for your enthusiasm and optimistic attitude.

Şermin Tükel, a fellow PhD student, for your contagious joy of life.

Johannes Breckenfelder for your determination, fighting spirit and never giving up. And for tough questions.

Stefan Gavelin for the inspiring ability to be open for changes and live life to the fullest.

Philip Cheong for your clear way of thinking, the ability to persuade and different perspective.

Ozan Alptekin for seeing the essential, for coming along with me and being the very special person, for your way of life and for the place in it. With you I learned to trust my instincts.

Thanks to my other friends in Sweden, Lithuania, The Netherlands and Denmark for their support and encouragement.

I am forever grateful to my parents, Lilijana Venskutonienė and Donatas Venskutonis for their foresight and values which influenced the course of my life and for the unconditional support along the way. Thank you for the values and the dreams you have given to me and letting me go along with them, not just this time, but so many times in my life.

Last, but not least, to Audas Jakaitis for an enormous amount of faith in me, your inexhaustible energy and all the wise words. It changed my perceptions of what is possible. I cannot thank you enough for everything that we have shared.

I thank one and all for making my dissertation journey a wonderful experience.

I would like to acknowledge the financial, academic and technical support of the Karolinska Institutet and the generous support of the Swedish Heart and Lung Foundation and AFA Insurance supporting me from the first steps in research to the birth of this book.

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